CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
Glyphosate

September 29, 2015

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

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EXECUTIVE SUMMARY

I. INTRODUCTION

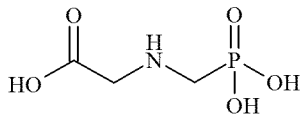
On September 16, 2015 the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of glyphosate.

II. BACKGROUND INFORMATION

Glyphosate (*N*-(phosphonomethyl) glycine) is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Tolerances are currently established for residues of glyphosate in/on various plant commodities at 0.2-400 ppm (40 CFR §180.364(a) (1). Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way.

The chemical structure and nomenclature for glyphosate is presented in Table 1.

Table 1. Chemical Nomenclature of Glyphosate

Compound	
Common name	Glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A.
The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed. In September 1993, the agency issued the glyphosate Reregistration Eligibility Decision (RED) document. Available from http://www.epa.gov/opp00001/chemsearch/reg action/reregistration/red PC-417300 1-Sep-93, pdf (D362745).

The carcinogenic potential of glyphosate has been evaluated by several regulatory authorities including the U.S EPA, European Union (EU), and the World Health Organization (WHO).

In 1985, the agency, in accordance with the Proposed Guideline for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical; Possible Human Carcinogen based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No.0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical; Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice was equivocal, they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). Available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division, Office of Pesticide Programs, in accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* classified glyphosate as a "Group E" chemical; evidence of non-carcinogenicity for humans. This classification was based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008898).

In 2002, the European Union (EU) concluded that there was no evidence of carcinogenicity for glyphosate in long-term studies with mice and rats (EU, 2002).

In 2004, the Joint FA0/WHO Meeting on Pesticide Residues (JMPR) concluded that there was no evidence of carcinogenicity for glyphosate in long term studies in mice and rats and there was no evidence for genotoxic potential (JMPR, 2004).

In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A chemical; Probable Human Carcinogen based on limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals. The limited evidence in humans was based on a positive association between non-Hodgkin's lymphoma and glyphosate exposure. The sufficient evidence in experimental animals was based on positive trend in the incidence of renal tubular carcinoma and of renal tubule adenoma/carcinoma combined in male CD-1 mice in one study and on the positive trend in the incidence of hemangiosarcomas in male CD-1 mice in another study (IARC, 2015).

In 2015, two chronic toxicity/carcinogenicity studies in rats (MRID Nos. 49631701 and 4970460) and one carcinogenicity study in mice (MRID No. 49631702) that were reviewed by IARC but previously not submitted to the agency, were submitted and reviewed. This weight of evidence assessment includes all the studies (epidemiology and experimental animals) reviewed by IARC.

III. EPIDEMIOLOGY

This section includes review of epidemiologic cohort and case-control studies of glyphosate and cancer to evaluate whether exposure to glyphosate is associated causally with risk of developing cancer in humans. The results of this review include studies of prostate, lung, and colorectal cancer in addition to less common cancers in the human population such as pancreatic and stomach cancer in association with pesticide use.

The Agricultural Health Study (AHS) is a large prospective study conducted in Iowa and North Carolina. Participants (private and commercial applicators) were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire (Alavanja *et al.,* 1996). The role of pesticide use and lymph hematopoietic cancers and particularly non-Hodgkin lymphoma (NHL) has been studied in several investigations. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available (De Roos *et al*., 2005); however, for NHL and other non-solid tumors, several investigations are published.

A. Cohort Studies

The eight cohort studies are discussed as "separate" studies; however, they are really separate analyses and publications from the same cohort of the AHS study (Alavanja *et al.,* 2003; Flower *et al*., 2004; DeRoos *et al*., 2005; Engel *et al*., 2005; Lee *et al*., 2007; Landgren et al., 2009; Andreotti *et al*., 2009; and Dennis *et al*., 2010). It should be noted that there is some overlap between the cases and person-time reported in the AHS.

B. Case-Control Studies

A total of 24 case-control studies were available for review.

Three case-control studies conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s were reported by Brown *et al.* (1990), Cantor *et al*. (1992) and Brown *et al.* (1993).

De Roos *et al*. (2003) and Lee *et al*. (2004a) reported the results of case-control studies conducted in Iowa, Minnesota, Nebraska and/or Kansas in the U.S.A.

The Canadian population based case-control studies were reported by (McDuffie *et al*., 2001; Hohenadel *et al*., 2011; Karunanayke *et al*., 2012; and Kachuri *et al*., 2013).

Results of the Swedish case-control studies were reported by Nordstrom *et al.*, 1998; Hardell and Erikson, 1999 and Hardell *et al*., 2002; and Eriksson *et al*., 2008).

A single case-control study conducted in France was reported by Orsi *et al.* (2009).

Coco *et al.*, (2013) reported the results of a pooled analyses of case-control studies conducted in six European countries between 1998 and 2004.

Case-control studies on the cancer of the brain (mainly gliomas) were reported by Ruder *et al.* 2004; Carreon *et al.*, 2005; Lee *et al.*, 2005; and Yiin *et al.*, 2012.

Case-control studies on other cancer sites were reported by Alavanja *et al.*, 2004 (lung); Bank *et al.*, 2011 and Koutros *et al.*, 2013 (prostate); Pahwa *et al.*, 2012 (soft tissue sarcoma) and Lee *et al.,* 2004b (stomach and esophagus).

Schinasi and Leon (2014) conducted a meta-analyses of the six studies that evaluated NHL and glyphosate exposure (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003; 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Sorahan (2015) conducted a re-analyses of the multiple myeloma in the U.S Agricultural Health Study.

C. Results

A summary of the studies evaluating the association between glyphosate and cancer are discussed below.

- Results of the studies reporting data on solid tumors (non- lympho-hematopoietic) at various anatomical sites are presented in Table 2.

- Results of the studies reporting data on glyphosate and non-solid tumors (lymphohematopoietic) are presented in Table 3.

1. Solid Tumor Cancer Studies

Within the AHS study cohort, a number of authors evaluated several anatomical cancer sites in relation to pesticide use. A discussion of studies outside of the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in Section C. 2 (Non-Solid Tumor Sites).

(i) Cancer at Multiple Sites

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence in the AHS cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. The authors used poisson regression to estimate exposure-response relationship between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtype. Exposure to glyphosate was not associated with all cancers combined [Odds Ratio (OR) =1.0 with 95% Confidence Interval (CI) of 0.90 - 1.2)] or specific anatomical cancer sites.

Several AHS nested case-control analyses also provide information concerning the carcinogenic potential of glyphosate; there is no statistical evidence of an association with glyphosate presented across these studies. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (Alavanja *et al.*, 2003; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005; Dennis *et al.*, 2010). The risk estimate odds ratios (OR) and 95% confidence indices for these studies are provided in **Table 2**.

In a population-based study (Band *et al*, 2011) outside to the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI= 0.83- 2.25). This study enrolled prostate cancer cases between 1983-1990, prior to the prostate-specific antigen (PSA) era; therefore, the study includes more advanced tumors upon diagnosis, and is not comparable to Alavanja *et al.* (2003), which reflects cases during the PSA-era in which cases are typically identified at an earlier stage in the progression of the disease. Notably, in a prostate cancer follow-up study within the AHS, Koutros *et al.* (2013) did not identify an association with advanced prostate cancer (OR=0.93; 95% CI=0.73 - 1.18).

A Canadian case-control study (Pahwa *et al.* 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with use of glyphosate (OR=0.90; 95% CI= 0.58-1.40)].

Flower *et al.* (2004) examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate: (OR=0.61; 95% CI= 0.32 - 1.16) or paternal (prenatal) exposure to glyphosate: (OR=0.84; 95% CI= 0.35 - 2.54)

(ii) Brain (Glioma) Cancer

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. The authors conducted telephone interviews of men and women diagnosed with gliomas (n = 251) between 1988 and 1993 in Nebraska and in controls (n = 498) identified from the same regions. Matching for age and vital-status, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI= 0.7 - 3.1) in relation to glyphosate use; however the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI= 0.1- 1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2 - 8.2), indicating recall bias was likely a characteristic of this study.

In other population-based case control studies of glioma risk authors investigated the question among men and also among women participating in the Upper Midwest Health Study (Carreon *et al.*, 2005; Ruder *et al.*, 2004; Yiin *et al.*, 2012). Among glioma cases identified 1995-1997, authors found little evidence of a role of glyphosate in the etiology of this tumor. While herbicide use

overall was non-statistically significantly linked to glioma in the study among men (OR=1.51; 95% CI= 0.92 - 2.48), use of glyphosate was not linked to glioma among women (OR 0.7 (95% CI (0.4, 1.3). In a study by Carreon *et al.* (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to the study by Lee *et al.* (2005) discussed above. Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (home and garden use: OR=0.98; 95% CI= 0.67 - 1.43); non-farm jobs: OR=0.83; 95% CI= 0.39 - 1.73) (Yiin *et al.*, 2012).

(iii) Stomach and Esophageal Cancers

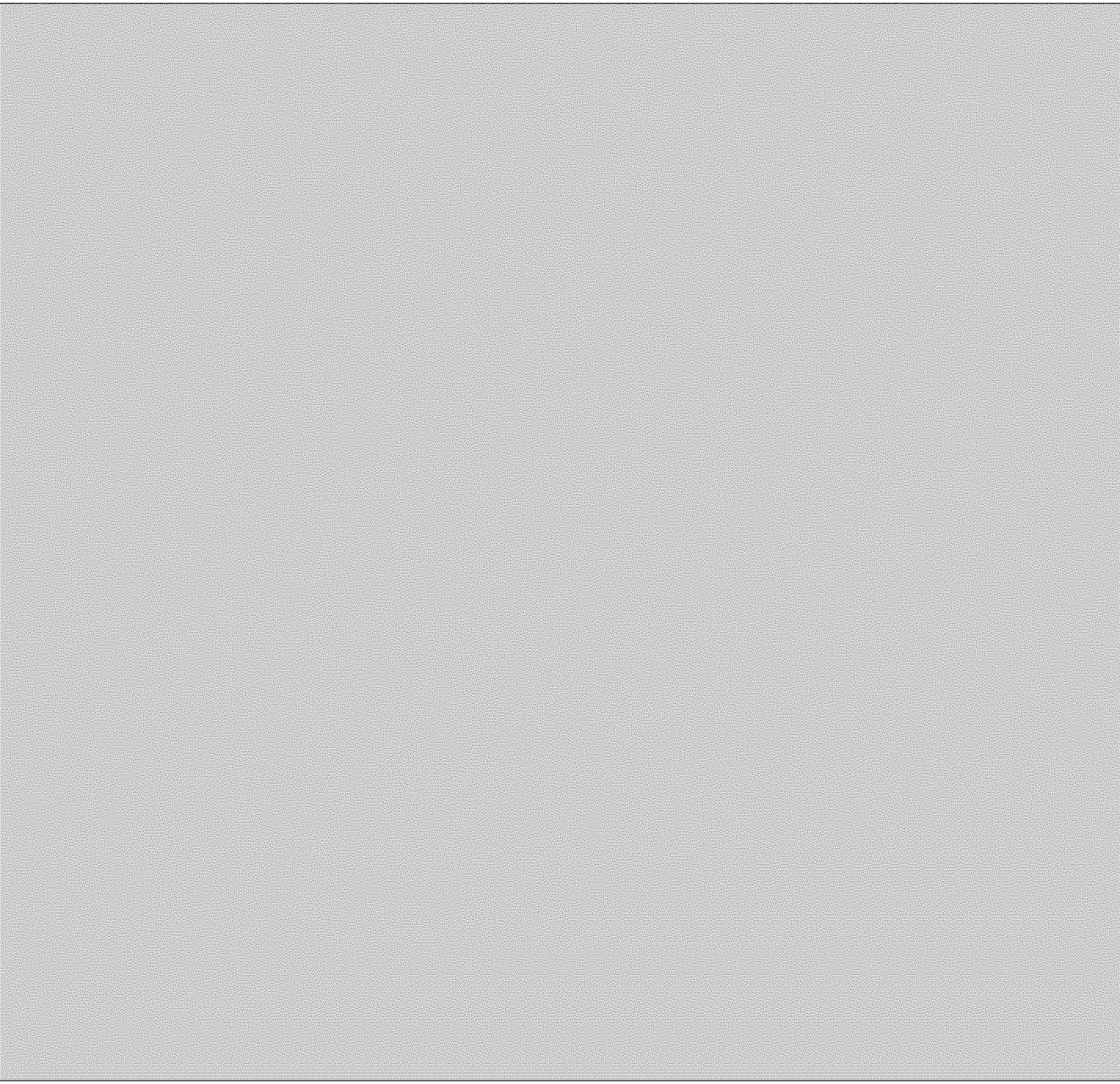
In a population based case control study in eastern Nebraska, Lee *et al.*, (2004) investigated pesticide use and stomach and esophageal adenocarcinomas. Cancer cases (stomach=170 and esophagus=137) were identified through the state cancer registry, and confirmed by pathologist. Exposure assessment was based upon self-report pesticide use, with follow-up telephone interview to verify reported information. There was no association between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI= 0.4 - 1.5) or esophageal cancer (OR=0.7; 95% CI= 0.3 - 1.4).

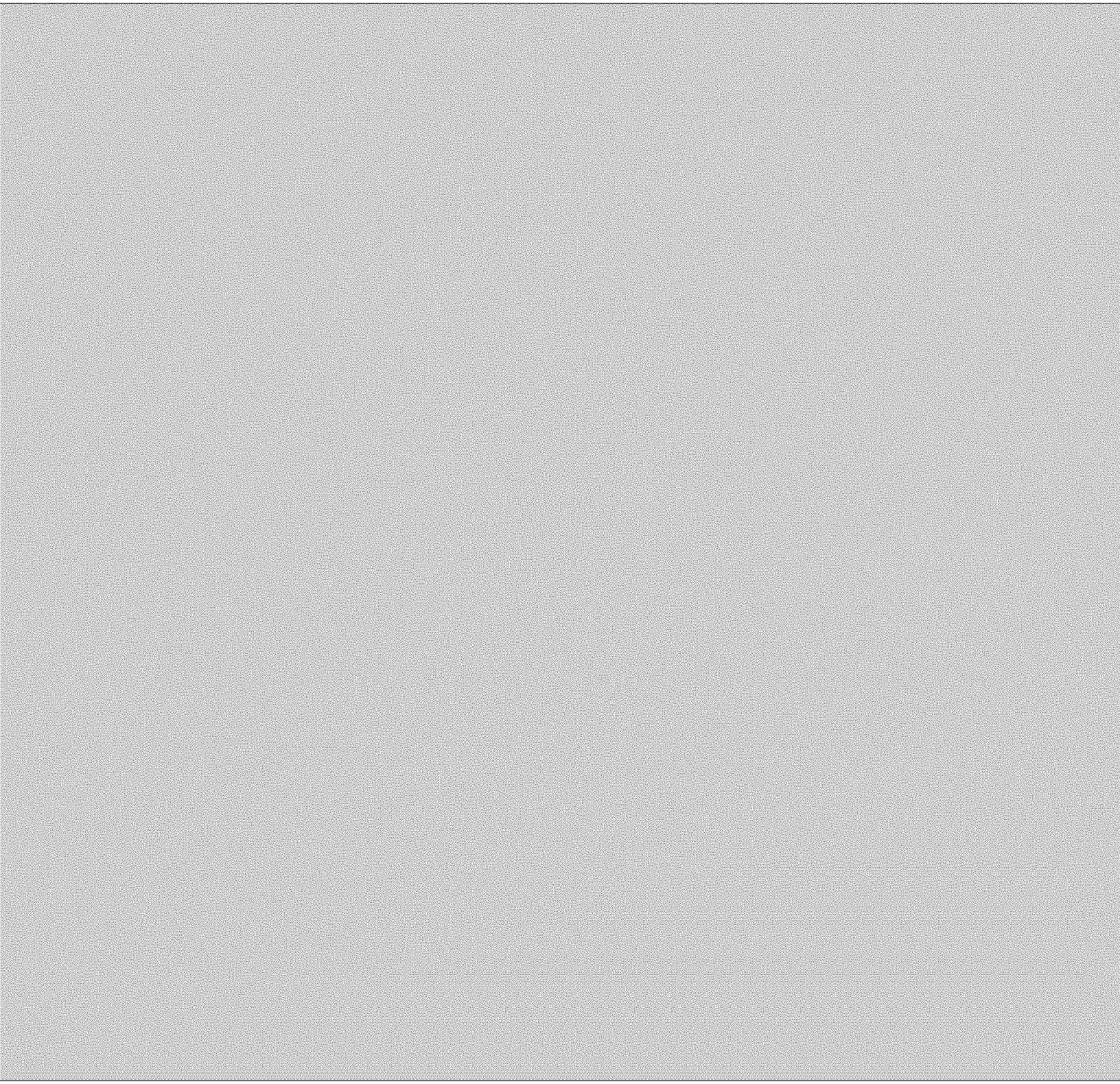
Site-Specific Cancers: Colorectal Cancer					
Lee *et al*. (2007) AHS: Iowa and North Carolina, U.S.A	Nested Case-Control 1993-97; follow-up to 2002	Self-report questionnaire	Colon OR=1.0; (0.7-1.5) (Exposed: 151 cases /49 controls) Rectum OR=1.6; (0.9-2.9) (Exposed: 74 cases/18 controls) Colorectal (OR=1.2; (0.9-1.6) Exposed: 225 cases/67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, total days use pesticides. Limited to licensed applicators. Potential exposure to multiple pesticides
Cancer at Multiple Sites					
De Roos *et al*. (2005) AHS: Iowa and North Carolina, U.S.A	Cohort 56,813 licensed pesticide applicators 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	All cancers OR = 1.0; (0.9-1.2) Colorectal (OR=1.2; (0.9-1.6) Exposed: 225 cases/67 controls) Oral Cavity OR=1.0; (0.5-1.8) Colon OR=1.4; (0.8-2.2) Rectum OR=1.3; (0.7-2.3 OR=0.7; (0.3-2.0)	No association between glyphosate exposure and all cancer including NHL.	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC.
Site-Specific Cancers: Lung; Oral cavity; Colon; Rectum; Kidney; Bladder; Prostate and Melanoma					
Site-Specific Cancers: Cutaneous Melanoma					
Dennis *et al*. (2010) AHS: Iowa and North Carolina, U.S.A AHS: Iowa and North Carolina, U.S.A	Nested Case-Control 1993-2001 1993-1997 54,315 licensed pesticide applicators 150 cases; 24,554 non-cases	AHS self-report questionnaire; validated, reliability tested; adjusted for other pesticides	OR= 0.9; (0.6-1.3) No quantitative risk estimate reported OR=0.90; (0.58-1.40)	No quantitative association between glyphosate exposure and cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate or cutaneous melanoma	Age, sex, tendency to burn, red hair, sum exposure time, BMI at 20 years (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)
Site-Specific Cancers: Soft Tissue Sarcoma					
Pahwa *et al*., (2011) Canada	Case-Control 1991-1994	Self-reported use, structured interview/ questionnaire; cumulative exposure	Kidney OR=1.6; (0.7-3.8) Bladder OR= 1.5; (0.7-3.2) Prostate	No association between glyphosate exposure and soft tissue sarcoma	Significant medical history variables and with strata for the variables of age group and providence of residence

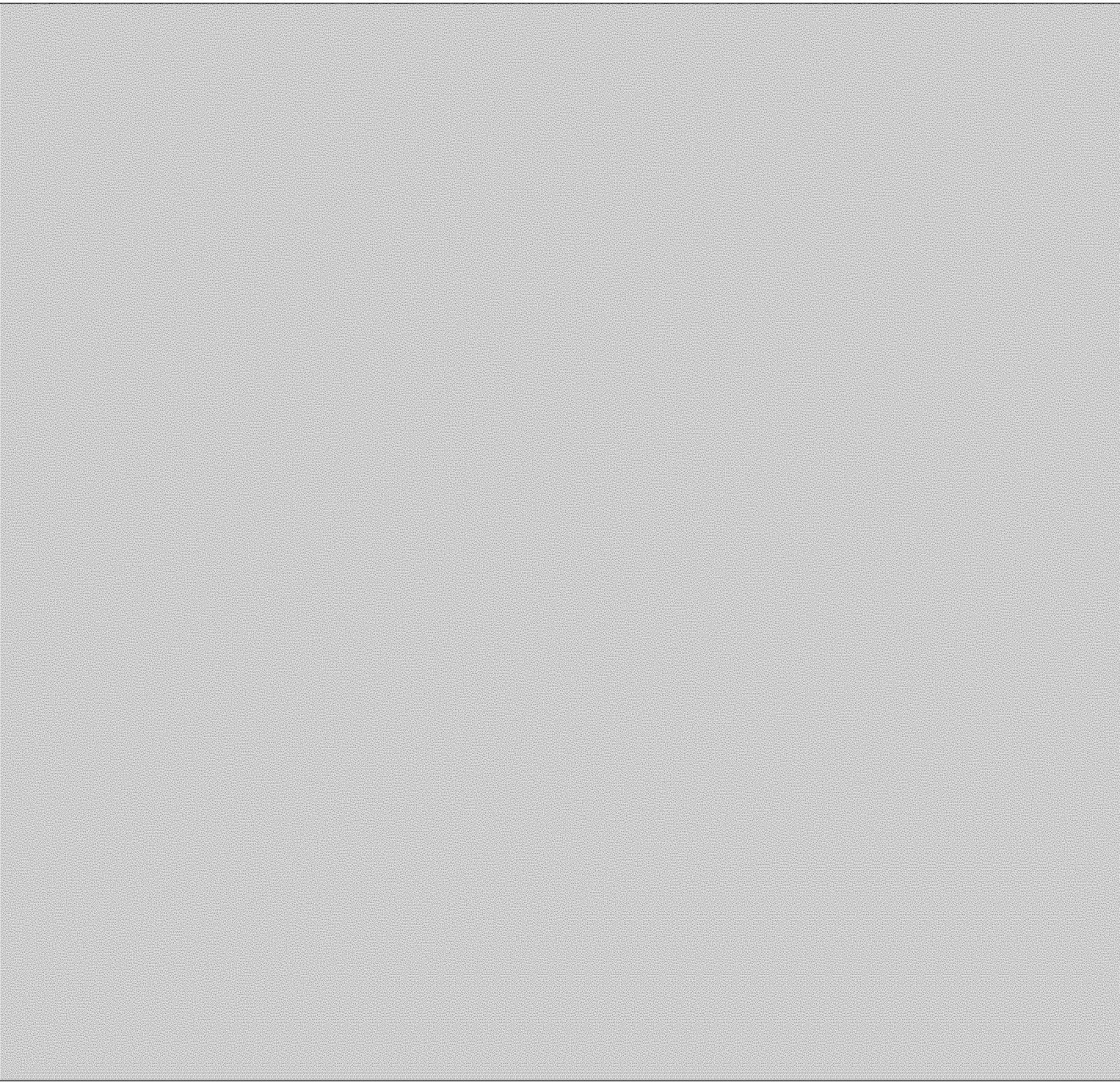
	342 cases, 1506 age/resident matched controls				
Total Childhood Cancer					
Flower *et al*. (2004) AHS: Iowa and North Carolina, U.S.A	Cohort; hybrid prospective/ retrospective 1993-1998 21, 375 children of licensed pesticide applicators In Iowa (n=17,357) North Carolina (n=4018)	Self-report questionnaire; duration and frequency of pesticide use; Female Family questionnaire (child name)	Maternal use OR =0.61; (0.32, 1.16) 32 exposed cases Paternal use (prenatal) OR=0.84; (0.35, 2.34);	No association was detected between frequency of parental pesticide application of glyphosate and childhood cancer risk.	Potential exposure to other pesticides. Child age in multiple logistic; [standardized incidence ratio (SIR)] was unadjusted
Brain Cancer (Glioma)					
Ruder *et al*. (2004) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin, U.S.A)	Population-based Case Control 1995-1997 457 glioma cases 648 population controls	Self-report questionnaire, with telephone based follow-up	No quantitative risk estimate reported for glyphosate.	No association with glyphosate exposure and brain cancer	Farm residence, age, use of other pesticides

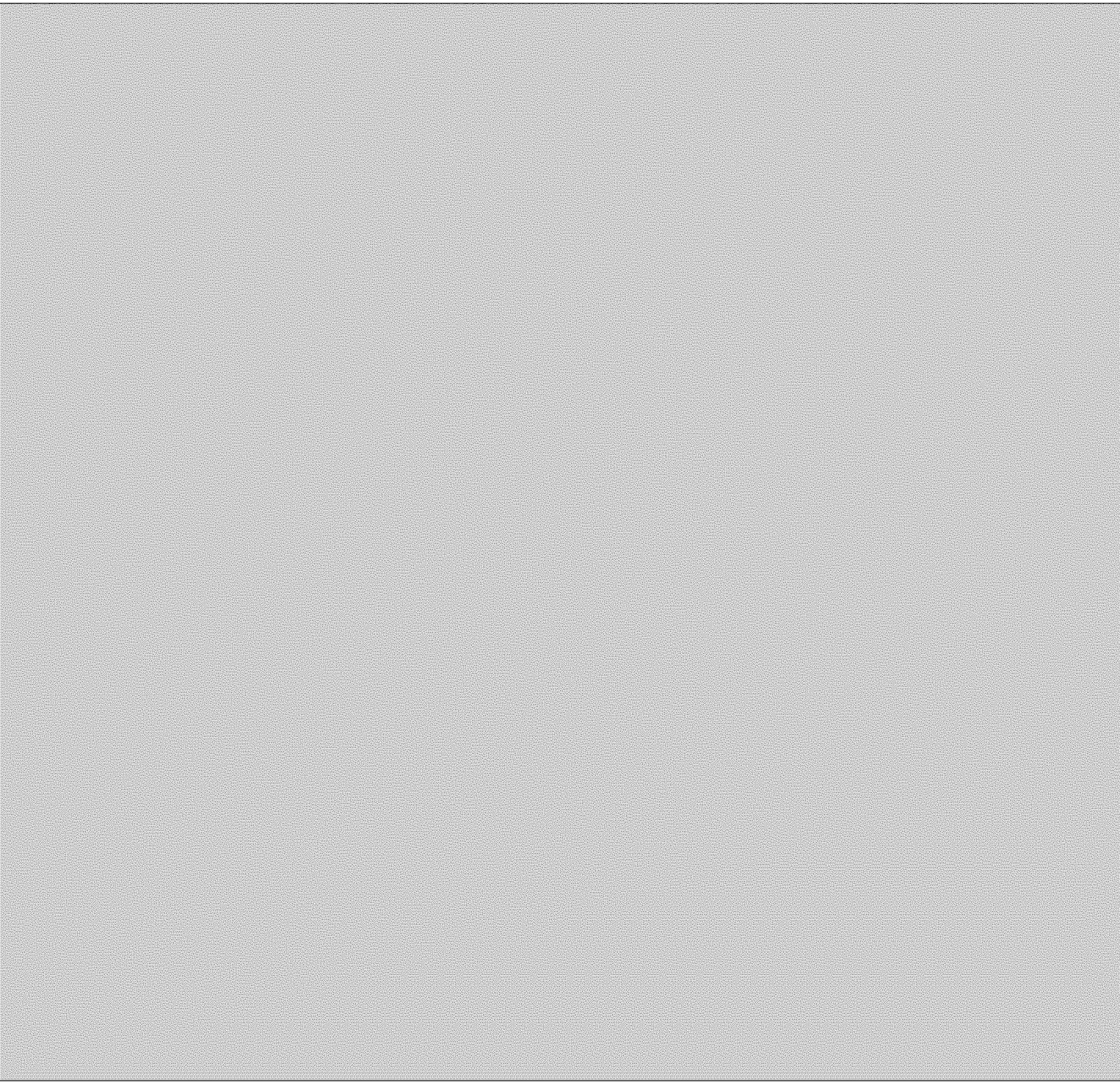
Carreon et al. (2005) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case Control 1995-1997 341 glioma cases, 528 controls	Self-report questionnaire	Proxy respondents OR=0.75; (0.4-1.3) Exposed: 18 cases 41 controls Excluding proxy OR=0.6; (0.3-1.2) 10 exposed cases	No association with glyphosate exposure and brain cancer	Age, education and use of other pesticide
Lee et al. (2005a) Nebraska	Population based Case Control study 1988-1993; 251 glioma cases 498 controls	Self-reported questionnaire information, telephone follow-up for unclear responses; men and women assessed separately	Self-Report OR=0.4; (0.1- 1.6) Exposed: 4 cases/17 controls Overall OR=1.5; (0.7-3.1) Exposed: 17 cases/32 controls Proxy report OR:=3.1; (1.2- 8.2) Exposed: 13 cases/15 controls	Non-significant excess risk for the overall group, but inconsistent for self-report and proxy indicating recall bias	Age, proxy, respond type
Esophagus and Stomach Cancer					
Lee et al. (2004b) Nebraska, U.S.A	Population based Case Control 1988-1993	Self-report pesticide use, telephone structured interview	Esophagus OR=0.7; (0.3-1.4) Exposed: 12 cases 46 controls Stomach	No association with glyphosate exposure and esophagus or stomach cancer	Age, sex

	137 esophageal cases; 170 stomach cases; 502 controls		OR=0.8; (0.4-1.5) Exposed: 12 cases 46 controls		









cific Breast	Glyphosate				

al. (2005)

va and North Carolina, U.S.A

ific Pancreatic	Glyphosate			DRAFT	

et al. (2009)

va and North Carolina, U.S.A

cific Prostate					

et al. (2003)

va and North Carolina, U.S.A

l. (2011) olumbia,	Case-Control 1983- 1990 1,516 prostate cancer patients 4,994 age-matched controls	Job exposure matrix for agriculture; detailed occupational history; exposure aggregated over all jobs reported. 60 exposed cases	OR=1.36; (0.83-2.25) (Exposed: 25 cases/60 controls)	No significant association between glyphosate exposure and prostate cancer	Alcohol consumption cigarette years, educa level, pip smoking ye respondent

t al. (2013)

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(2007) va and North U.S.A	Nested Case-Control 1993-97; follow-up to 2002 56,813 licensed pesticide applicators	Self-report questionnaire	Colon OR=1.0;(0.7-1.5) (Exposed: 151 cases /49 controls) Rectum OR=1.6; (0.9-2.9) (Exposed: 74 cases/18 controls) Colorectal (OR=1.2; (0.9-1.6) Exposed: 225 cases/67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, t use pesticides. Limite licensed applicators. F exposure to multiple p
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al. (2010) va and North U.S.A	Nested Case-Control 1993-1997 150 cases, 24,554 non-cases	AHS self-report questionnaire	No quantitative risk estimate reported	No quantitative estimate due to lack of an association with cutaneous melanoma	Age, sex, tendency to red hair, sum exposur BMI at 20 years
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, U.S.A	1988-1993 Glyphosate 137 esophageal cases; 170 stomach cases; 502 controls		46 controls Stomach OR=0.8; (0.4-1.5) Exposed: 12 cases 46 controls	stomach cancer	

2. Non-Solid Tumor Sites (Lymph hematopoietic Cancers)

A number of studies evaluating the possible link between pesticide use and lymphohematopoietic cancers such as leukemia, multiple myeloma and NHL are presented in **Table 3**.

(i) Leukemia

In a population-based case control study in Iowa and Minnesota, Brown *et al.* (1990) investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR= 0.9; 95% CI = 0.5 -1.6). The study population (578 cases; 340 living and 238 deceased and 1245 controls) was identified from cancers reported to state registry or authorities in 1981-1984, and pesticide exposure assessment was performed through in-person interview which authors state likely reduced exposure misclassification (incorrect exposure information). Although the large sample size is a strength of this study, the limitations include not controlling for exposure to other pesticides, limited power for studying the effects of glyphosate use, and the potential for recall bias.

In a Swedish population based case control study, 121 cases in men and 484 controls matched for age and sex were identified in 1987-1992 through the Swedish cancer registry (Nordstrom *et al.*, 1998). Authors reported a non-statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR=3.1; 95% CI= 0.8 -12.0), controlling for age, sex, and residential location. However, these results are based on only 4 glyphosate exposed cases and 5 exposed controls and should be interpreted with caution as noted by the investigators. Also, there was limited power to detect an effect and there was no adjustment for other exposures. At this time, there is limited available literature concerning glyphosate use and leukemia.

(ii) Multiple Myeloma

In a follow-up analyses using the same study population from Iowa and Minnesota, Brown *et al.* (1993) investigated whether pesticide use is also related to multiple myeloma. Among men in Iowa (173 cases, 605 controls), authors observed a statistically non-significant elevated association with glyphosate use (OR=1.7; 95% CI = 0.80 - 3.6). However, authors caution that while the study may lend support for the role of pesticides in general, the study limitations preclude use of evidence in support of any one compound.

De Roos *et al.* (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on a small number (32) of cases. For applicators with the full data set (54,315) and without adjustment for other variables the OR was 1.1; 95% CI, 0.5 – 2.4. In the fully adjusted models, , there was a non-statistically significantly elevated risk (OR= 2.6; 95% CI= 0.70 - 9.4), however, the number of participants included in this analysis was lower (n=40,716) due to missing data for the covariates. The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses.

Lash *et al* (2007) performed a bias analysis of the De Roos *et al* (2005) data and reported that the frequency distribution generated by the bias analysis yielded a median hazard ratio equal to 1.5 with 95% simulation interval of 0.4 to 8.9, which was 66% wider than the conventional interval.

Sorahan (2015) using Poisson regression, re-analyzed the AHS data reported by De Roos *et al.* 2005) to examine the reason for the disparate findings in relation to the use of full data set versus the restricted data set. Risk ratios were calculated for exposed and non-exposed subjects. When adjusted for age and sex, the OR was 1.12 with the 95% CI of 0.5 – 2.49 for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of other pesticides did not have any effect (OR=1.24; 95% CI= 0.52 – 2.94).

In a population-based case control study among men in six Canadian provinces between 1991 and 1994, researchers reported non-statistically significantly elevated odds of multiple myeloma in relation to glyphosate use (OR=1.22; 95% CI= 0.77 - 1.93), based upon 32 glyphosate exposed multiple myeloma cases and 133 controls (Pahwa *et al.*, 2012).

Kachuri *et al.* (2013), using the same Canadian study population as above, further explored multiple myeloma in relation to days per year used glyphosate in 342 cases of multiple myeloma and 1357 controls. For ever use, the OR=1.19; 95% CI=0.76-1.87. For light users (≤2 days/ year) there was no association (OR= 0.72; 95% CI= 0.39 -1.32; 15 exposed cases) whereas for heavy users (>2 days/ year) there was a non-significant increased odds (OR= 2.04; 95% CI=0.98-4.23; 12 exposed cases). The limitation in this study was just as in the previous study namely, the number of cases and controls exposed to glyphosate were very low.

Landgren *et al.* (2009), within the AHS study population investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS); MGUS is considered a pre-clinical marker of multiple myeloma progression. Authors did not observe a link with glyphosate use in the AHS cohort (OR= 0.50; 95% CI = 0.20 -1.0)

(iii) Lymphoma

The National Cancer Institute (NCI) performed a series of population based case control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred non-Hodgkin lymphoma (NHL) cases and controls; the identified cases were through disease registries which in many cases were histopathologically confirmed. Investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time.

Cantor *et al* (1992), in a case-control study of NHL interviewed a total of 622 white men and 1245 population based-controls in Iowa and Minnesota. Only 26 cases and 49 controls ever handled glyphosate yielding an OR= 1.1 with the 95% CI of 0.7 – 1.9. The study, however, did not adjust for exposure to other pesticides.

De Roos *et al.*, (2003) used pooled analysis (n=3,417) of three case-control studies of NHL

conducted in Nebraska, Kansas and in Iowa and Minnesota. Based on 36 exposed cases and 61 exposed controls, the risk estimates for the association between glyphosate exposure and NHL was 2.1 (95% CI=1.1-4.0) in the logistic regression analyses. Utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, there was an increase risk, but the increase was not statistically significant (OR= 1.6; 95% CI = 0.90 - 2.8).

Lee *et al.*, (2004) examined the relationship between asthma, pesticide exposure, and, NHL. Pooling data from several Midwestern (IA, MN, NE) states increased the study sample size, and additional pesticide use information was incorporated to adjust the risk estimate (duration and frequency of use, telephone follow-up interview). The study included 872 men with NHL and 2381 frequency-matched controls. The authors reported that the OR associated with glyphosate was not statistically significantly different among those with asthma (OR=1.2; 95%CI=0.4 -3.3; 6 exposed cases) and among those without asthma (OR=1.4; 95% CI =0.98 - 2.1; 53 exposed cases), adjusting for age, state and vital status.

The three studies discussed above (Cantor *et al.*, 1992; De Roos *et al.*, 2003 and Lee *et al.*, 2004) reflect the same population in the AHS and used different levels of information (duration and frequency of exposure) and different analytic techniques [hierarchical regression and stratified analysis (by atopy)]. While studies with increasing levels of refinement to method report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

A population-based case–control study (Hardell and Erickson, 1999) investigated the exposure to pesticides as risk factor for NHL in Sweden during 1987-1990. Exposure data were ascertained by comprehensive questionnaires and supplemented by telephone interviews. Of the 404 cases and 741 controls, only 4 glyphosate exposed cases and 3 controls were included in the study. In a univariate analysis, the risk estimate was elevated, but precision was low (OR= 2.3; 95% CI= 0.40 - 13.0).

Hardell *et al.* (2002) analyzed pooled data from two case-control studies from Sweden that examined NHL (Hardell and Erickson, 1999) and another on hairy cell leukemia, a subtype of NHL (Nordstrom *et al.*, 1998). In the univariate analysis glyphosate exposure was found to increase risk (OR=3.04; 95%CI=1.08-8.52 but, when study, study area, and vital status were considered in a multivariate analyses, there was a non-statistically elevated risk among glyphosate users (OR = 1.85; 95% CI= 0.55 - 6.20).

In another case-control study in Sweden (1999-2003), Eriksson *et al.* (2008) examined the effects of exposure to different agents and NHL among 910 NHL cases and 1016 non-NHL controls. Glyphosate which was reported by 29 cases and 18 controls produced an OR of 2.02 and 95% CI of 1.10–3.71 in a univariate analysis and an OR of 1.51 and 95% CI of 0.77–2.94 in a multivariate analysis conducted to clarify the relative importance of exposure to different pesticides. Risk estimate was elevated also for B-cell lymphoma and glyphosate exposure (OR=1.87; 95% CI=0.998-3.51).

McDuffie *et al* (2001) in a multicenter-population based study among men of six Canadian provinces estimated the association between glyphosate and NHL. The study included 517 cases and 1506 controls identified betwen1991and 1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, and implemented a two-tiered exposure questionnaire, and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the study results. There was a non-statistically significant increased risk (20%) of NHL from glyphosate exposure. The OR was 1.26 and the 95% CI was 0.87–1.80 for 51 exposed cases, adjusted for age and province and the OR was 1.20 with a 95% CI of 0.83–1.74 when adjusted for age, province and high-risk exposure (adjusted for statistically significant medical variables such as history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative).

In a follow-up study which controlled for exposure to other pesticides, the risk to NHL from glyphosate exposure was attenuated. Glyphosate which was reported by 19 cases and 78 controls produced an OR of 0.92 with 95% CI of 0.5–1.55 (Hohenadel *et al.*, 2011). Within this series of studies, authors also evaluated Hodgkin's lymphoma (HL), and similarly observed little statistical evidence of an association, using similar study design and methods. Among the 38 cases exposed to glyphosate the OR was 0.99 with the 95% CI of 0.62 - 1.56 (Karunanayake *et al.,* 2012).

In a hospital-based case control study conducted between 2000 and 2004 in France, authors identified 491 NHL cases and 456 age-and sex-matched controls, and performed telephone-based questionnaire to assess pesticide and other confounding variables. There was no association between NHL and glyphosate use; for the 12 exposed cases, the OR was 1.0 and the 95% CI was 0.50 - 2.2) (Orsi *et al.*, 2009).

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and lymphoma, B-cell lymphoma and subtypes. Although the study recruited 2348 cases and 2462 controls, very small number of cases were exposed to glyphosate (n=4) and controls (n=2). A non-significant increase in OR was observed for B-cell lymphoma (OR=3.1; 95% CI= 0.6-17.1), but the estimate is unstable due to small number of exposed cases and controls (Cocco *et al.* 2013)

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL utilizing six of the above mentioned studies (McDuffie *et al.* 2001; Hardell *et al.* 2002; DeRoos *et al.* 2003 and 2005; Eriksson *et al.* 2008; and Orsi *et al.* 2009). Since the authors identified a variety of sources of heterogeneity between publications, they calculated meta-risk ratio (RR) estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. They reported I^2 values, which represented the percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. For glyphosate, the meta risk-ratio was 1.5 with a 95% CI of 1.0-2.0 and the I^2 value was 32.7%.

This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences.

The 2015 IARC evaluation noted that two of the Swedish studies' (Hardell *et a*l. 2002 and Eriksson *et al*. 2008) fully adjusted risk estimates were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, IARC conducted a reexamination of the results of these studies. For an association between glyphosate exposure and NHL, the IARC estimated meta-risk ratio of 1.3 (95% CI was 1.03-1.65), I^2= 0%, p=0.589, for heterogeneity (IARC 2015).

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Leukemia					
Brown *et al.* (1990) Iowa and Minnesota, U.S.A	Population based Case-Control 1981-1984 578 cases 1245 controls	In person interview; surrogates used.	OR=0.9; (0.5-1.6) Exposed: 15 cases 49 controls	No association with glyphosate exposure and leukemia	Vital status (alive, dead), residency (IA or MN), tobacco use, parent, sibling, or child with a lymphopoietic cancer, high risk occupation and exposure to substances (benzene, hair dyes etc) related to risk of leukemia
Nordstrom *et al.* (1998) Sweden	Population based Case-Control 1987-1992 121 cases 484 controls	Self-reported pesticide questionnaire and follow-up telephone interview	OR=3.1 (0.8-12) Exposed: 4 cases 5 controls	A non-statistically significant elevated risk of hairy cell leukemia.	Age, sex country of residence (selected using matching, dissolved matching analyses). No adjustment for exposure from other pesticides
Multiple Myeloma					
Brown *et al.* (1993) Iowa, U.S.A	Population based Case-Control 1981-1984 173cases	Interview based questionnaire with follow-up	OR=1.7; (0.8-3.6) Exposed: 11 cases 40 controls	Limited power to assess association of glyphosate exposure and multiple myeloma	Age and vital status

Glyphosate	650 controls		DRAFT		
De Roos *et al*. (2005) Iowa and North Carolina, U.S.A	Prospective Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	Full data set OR =1.1; (0.5 – 2.4) Exposed: 32 cases Adjusted for age etc OR=2.6; (0.7-9.4)	No risk for full data set. Excess risk only with no missing information of 22 cases in the restricted data set (Sorahan, (2015)	Missing data on covariates when multiple adjustments were made, limiting interpretation.
Orsi *et al*. (2009). France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=2.4; (0.8-7.3) Exposed: 5 cases/18 controls	No significant association with glyphosate exposure and multiple myeloma	Age, center, socioeconomic category
Pahwa *et al*. (2012) Canada	Population based Case-Control 1991-1994 342 cases 1506 controls	Self-reported pesticide use, structured interview with questionnaire; cumulative exposure (+/-10 days/yr),	OR=1.22; (0.77 - 1.93) Exposed: 32 cases 133 controls	No significant association with glyphosate exposure and multiple myeloma	Significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree

					relative), and with strata for the variables of age group and province of residence.
Kachuri *et al.* (2013) Canadian Provinces	Population based Case-Control 1991-1994 342 cases 1357 controls	Self-administered questionnaire	<u>For ever use</u> OR=1.19; (0.76-1.87) Exposed: 32 cases/121controls <u>Light (<2 d/yr) use</u> OR= 0.72; (0.39 -1.32) Exposed: 15 cases/88 controls <u>Heavy (>2 d/yr) use</u> OR=2.04; (0.98-4.23) Exposed: 12 cases/29 controls	No association with glyphosate exposure and multiple myeloma for ever or light users Increase for heavy users is non-significant	Relatively low response rate
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren *et al.* (2009) AHS: Iowa and North Carolina, U.S.A	Prospective Cohort study 1993-1997 678 participants	Self-administered questionnaire	OR=0.5; (0.2-1.0)	No association with glyphosate exposure and MGUS, a premalignant disorder that often precedes multiple myeloma	Age and education
Non Hodgkins Lymphoma (NHL)					
Cantor *et al.* (1992) Iowa and Minnesota, U.S.A	Population based Case-Control 1980-1983	Structured interview, questionnaire response; farm activities and specific pesticide use	OR=1.1; (0.7-1.9) Exposed: 26 cases 49 controls	No association with glyphosate exposure and NHL	Vital status, age, state, smoking, family history, high risk occupation, high risk exposure. Not controlled for exposure to other pesticides.

Glyphosate	622 cases 1245 controls		DRAFT		

De Roos *et al.* (2003) Iowa, Nebraska, Minnesota, Kansas, U.S.A	Case-Control 1983-1986 870 cases 2569 controls	Interview-based questionnaire, demographic	Logistic regression OR=2.1; (1.1-4.0) Exposed: 36 cases 61 controls Hierarchical regression OR=1.6; (0.9-2.8)	No significant association with glyphosate exposure and NHL The increase in OR is not statistically significant	Age, study site, use of all other pesticides (group); hierarchal regression informed priors based on chemical-specific information
Lee *et al*., (2004a) Iowa, Nebraska, Minnesota, U.S.A	Population based Case-Control 1980-1986 872 cases 2381controls	In person, structured interview (pesticide use, duration, frequency, first and last year used); 5-yr follow-up interview, 10-min telephone on pesticide use	Non-asthmatic OR=1.4; (0.98-2.1) Exposed: 53 cases 91 controls Asthmatic OR=1.2 (0.4-3.3) Exposed: 6 cases 12 controls	No significant association with glyphosate exposure and NHL either for asthmatics or non-asthmatics.	A adjusted for age, vital status, state
Hardell and Erickson, (1999) Sweden	Population based Case-Control 1987-1990 404 cases 741 controls	Questionnaire and follow-up interview	Univariate OR=2.3; (0.4-13.0) Exposed: 4 cases 3 controls Multivariate OR=5.8; (0.6-54)	Some evidence of a link with glyphosate, matching variables; cannot conclude regarding causal role for any specific pesticide	Age, region, vital status (matching). Few subjects exposed. Variables used in multivariate were no specified. Study has limited power to detect an effect
Hardell *et al*. (2002) Sweden	Population based Case-Control 1987-1990 515 cases	Questionnaire and follow-up interview	Univariate OR=3.04; (1.08-8.52) Exposed: 8 cases 8 controls	Risk attenuates when adjusted for other variables in the multivariate analysis	Age, country, study site, vital status, other pesticide exposure in the multivariate analysis. Overlaps with Hardell and Erickson, 1999

Glyphosate	1141 controls		Multivariate OR=1.85; (0.55-6.20)	DRAFT	and Nordstrom et al., 1998.
Eriksson *et al*. (2008) Sweden	Population based Case-Control 1999-2002 910 cases 1016 controls	Questionnaire and follow-up interview	Univariate OR= 2.02 (1.10-3.71) Exposed: 29 cases 18 controls Multivariate OR=1.55; (0.772.94) With <10 days/ year OR=1.69; (0.7-4.07) Exposed: 12 cases/9 controls With > 10 days/year OR=2.36; (1.04-5.37) Exposed: 17 cases/9 controls B-cell lymphoma OR=1.87; (0.998-3.51)	Glyphosate was associated with a statistically significant Increased OR for lymphoma.	Age, sex, year of diagnosis. Multivariate analysis adjusted for exposure to other pesticides
McDuffie *et al* (2001) Canada	Population based Case-Control 1991-1994	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	Univariate OR=1.26; (0.87-1.8) Exposed: 51 cases 133 controls	No significant association with glyphosate exposure and NHL	Adjusted for statistically significantly medical variables (history of measles, mumps, cancer, allergy shots, and a

	517 cases 1506 controls		Multivariate OR=1.20; (0.83-1.74)		positive family history of cancer)
Hohenadel *et al.* (2011) Canada	Case-Control 1991-1994 513 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	OR=0.92; (0.54-1.55) Exposed: 19 cases/78 controls	No association with glyphosate exposure and NHL	Age, province and proxy respondent.
Karunanayake *et al.,* (2012). Canada	Case-Control 1991-1994 361 cases 1,506 controls	Questionnaire and follow-up interview	Univariate OR=1.14;(0.74-1.76 Exposes: 38 cases/133 controls Multivariate OR=0.99; (0.62-1.56)	No association with glyphosate exposure and NHL	History of measles, acne, hay fever, shingles and positive family history of cancer in a first-degree relative
Orsi *et al*. (2009). France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	NHL OR=1.0; (0.5-2.2) Exposed: 12 cases/24 controls Hodgkins Lymphoma OR=1.7; (0.6-5.0) Exposed: 6 cases/15 controls	No association with glyphosate exposure and NHL	Age, center, socioeconomic category

Glyphosate			Multiple Myeloma OR=2.4, (0.8-7.3) Exposed: 5 cases/18 controls	DRAFT	
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain	EPICLYMPH Case-Control 1998–2003 2348 cases 2462 controls	Occupational exposure Trained interviewers conducted in person interviews with cases and controls, using the same structured questionnaire translated into the local language	OR=3.1; (0.6-17.1) Exposed: 4 cases/2 controls	No significant association with glyphosate exposure and B-cell	Age, centre, socioeconomic category.
Hodgkin's Lymphoma					
Orsi *et al.* (2009). France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.7; (0.6-5.0) Exposed: 6 cases/15 controls	No significant association with glyphosate exposure and HL	Age, center, socioeconomic category

D. Discussion

In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. During their life time, farmers are typically exposed to multiple pesticides and several of them are used together posing a challenge for identifying specific risk factors. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, it can be subjective to misclassification and recall bias. For example, case-control studies are at risk of recall bias in the reporting of pesticide use in the past. The possible effect of confounding factors which are related to both the exposure of interest and the risk of disease may make it difficult to interpret the results. Therefore, the ability of epidemiologic studies to provide convincing evidence of causation under such circumstances may be limited. Causation is suspected if several studies are consistent in their findings; if the association between the agent and the risk of disease is strong (i.e, high OR). Support from animal data will help to make the case for causation, particularly by establishing biologic plausibility and the existence of potential mechanism. Another important component that should be factored in assessing epidemiologic studies is the fact that a commercial formulated product (not the active ingredient) is used by farmers. Glyphosate is sold as Roundup which is a combination of the active ingredient and other chemicals including a surfactant (polyethyleneamine) used to enhance the spreading of spray droplets when they contact the foliage.

Most of the studies discussed here were hypothesis-generating in nature, small sample sizes with limited power to detect associations, and study authors evaluated use of glyphosate in addition to several other pesticides. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis limit epidemiologic inference. These hypothesis-generating studies require further follow-up studies to determine whether the true association with glyphosate is indeed null.

Several population-based case-control studies have evaluated exposure to pesticides, including glyphosate, as a risk factor for NHL. While some studies observed non-statistically significantly increased risk of NHL in relation to glyphosate use, others reported no such association with glyphosate use. Strong dose response relationships were generally absent; most analyses that examined associations with multiple categories of exposure derived imprecise estimates with wide confidence intervals.

The first report of an association of glyphosate with NHL was based on only four exposed cases (Hardell and Erickson, 1999). A Canadian study reported a non-significantly increased risk of NHL association with glyphosate (McDuffie *et al.*, 2001) which attenuated in a follow-up study when controlled for exposure to other pesticides (Hohenadel *et al.*, 2011).

A Swedish study reported a non-statistically significant odds ratio of NHL among glyphosate users (Hardell *et al.*, 2002). An elevated but non-statistically significant result was also reported in a large study in the U.S. when exposure to other pesticide exposure was utilized in a hierarchical regression analysis (De Roos *et al.*, 2003). Only one author (Erikson *et al.*, 20028) reported a statistically significant association of NHL with lifetime use of glyphosate. The finding in this study, however, should be evaluated further for study bias, confounders and sampling errors.

In the large prospective cohort study (AHS), there was no association with glyphosate use and NHL. AHS also found no association between glyphosate use and incidence of all cancers combined and 12 relatively common anatomical cancer sites. There was, however, a suggested association with multiple myeloma which needs follow-up. Other studies showed no association of glyphosate use and an association for cancers of the brain, esophagus, stomach, prostate, soft-tissue sarcoma, multiple myeloma or between frequency of parental pesticide application of glyphosate and childhood cancer risk.

The case-control studies discussed above are retrospective studies and are susceptible to recall bias of exposure reporting which could account for discrepancy in the study findings. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could explain these inconsistencies in the data. In contrast, a prospective cohort study evaluates a number of diseases simultaneously and facilitates performance of periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures enhances recall and reduces nondifferential misclassification. The ability to determine exposure prior to the onset of a disease eliminates the case-recall bias, an issue identified as weakness in case-control studies.

E. Conclusion

There was no association with any site-specific cancer including NHL and lifetime use of glyphosate in 57,311 pesticide applicators in Iowa and North Carolina (De. Roos *et al.*, 2005).

No association was found for cancer of the oral cavity, colorectum, lung, pancreas, kidney, bladder, prostate, breast or melanoma (De Roos *et al.*, 2005; Engle *et al.*, 2005; Lee *et al.*, 2007; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010).

In single case-control study, no associations were found for cancers of the esophagus, stomach, prostate or soft-tissue sarcoma from exposure to glyphosate (Lee *et al*, 2004; Band *et al.*, 2011; and Pahwa, *et al.*, 2011).

The Upper Midwest Health case-control study found no association of glyphosate with adult brain cancer (Ruder, 2004; Carreon *et al.*, 2005; and Lee *et al.*, 2005).

No excess in leukemia was reported in a case-control study in Iowa and Minnesota (Brown *et al.*, 1990) or in the AHS study (De Roos *et al.*, 2005).

The increased risk for multiple myelomas did not reach statistical significance and the possibility of chance could not be excluded (Brown *et al.*, 1993; De Roos *et al.*, 2005; Orsi *et al.*, 2009; Kachuri *et al.*, 2013; and Sorahan, 2015).

In the case-control study in the midwestern United States, after adjustment for exposure to other pesticides, the elevated odds ratio did not reach statistical significance (De Roos *et al,* 2003).

A hospital based case-control study from France did not find an association between glyphosate exposure and NHL (Orsi *et al.*, 2009).

In the case-control study in Canada, there was a non-statistically significant increased risk of NHL; however, the risk attenuated when controlled for exposure to other pesticides (McDuffee *et al.*, 2011; Hohenadel *et al.* 2011).

In a case-control study from Sweden, there was a non-statistically significantly elevated risk among glyphosate users (Hardell 2002).

A statistically significant increase in NHL with glyphosate exposure was reported in a single case-control study in Sweden (Erickson *et al.*, 2008).

In contrast, the large AHS cohort study in the U.S with 57,311 pesticide applicators in Iowa and North Carolina did not corroborate the positive association observed in the study in Sweden (De Roos *et al.*, 2005)

In summary, there was no association with any site-specific cancer or NHL and lifetime exposure to glyphosate in the large prospective cohort study of 57,311 licensed pesticide applicators in AHS. There was no consistent patterns of statistically significant positive association between glyphosate exposure and NHL. A statistically significant positive association for NHL and glyphosate exposure was reported in one Swedish case-control study. The finding in this study, however, should be evaluated further for study bias, confounders and sampling errors before establishing causality. However, a meta-analysis utilizing six of the above studies examining glyphosate and NHL found a significant increased meta risk ratio (Schinasi and Leon, 2004).

In assessing the weight-of-evidence of epidemiologic studies which relate to glyphosate exposure, one has to make a subjective judgment as to the weights given for the various studies and their conflicting conclusions. There are different results from many of the studies; some have shown a relationship between glyphosate and NHL and some did not observe an association. However, there are inconsistencies in the results (even of the positive Swedish study) which raise doubts as to whether the relationship is causal with the current status of the literature. A large cohort study did not show an association with NHL. Therefore, taken together, the current state of the epidemiological literature does not support a causal association between glyphosate and the risk of non-Hodgkin's lymphoma or any site specific cancer. However, after, combining six of the smaller case-control studies in a meta-analysis, a significant increased meta risk ratio was detected. Thus,

while the epidemiologic literature to date does not support causal association, continued following of the glyphosate and NHL literature is warranted. Furthermore, there is no support from animal data to make the case for causation, particularly by establishing biologic plausibility and the existence of potential mechanism since there was no evidence for carcinogenicity twelve studies conducted in mice or rats (discussed below)

IV. EVALUATION OF CARCINOGENICITY IN ANIMALS

A total of 12 chronic toxicity/carcinogenicity studies (7 studies in rats and 5 in mice) were included in this weight of evidence review. Of these, 6 studies (4 rat and 2 mouse) were submitted for review to EPA under registration/reregistration program. Data for review of the other 6 studies were obtained from a review article by Greim *et al.*, 2015. Each study reported in this review article was evaluated in accordance with the agencies 2012 Guidance for considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf). In accordance with the 2012 guidance, the following studies were not included in this review:

- A two year feeding study in rats (Excel, 1997) was not included due to the lack of test article characterization (no purity) and lower than expected background tumor incidences.

- The study reported by Chruscielska *et al.*, (2000) was not included since the tested material was a formulated product (13.6% ammoniuum salt) in drinking water and a number of deficiencies (lack of purity, water consumption and body weight data) in the conduct and reporting of that study.

- An initiation-promotion study (George *et al*, 2010) in male Swiss was not included since the test material was a commercial formulation of glyphosate (41%) with deficiencies in the conduct [small number (20) of animals, tested only males, no data on solvent controls, and lack of histopathological examination] of that study.

A. Studies in Rats

1. Lankas, G, P. A Lifetime Study of Glyphosate in Rats. December 23, 1981. Unpublished report No. 77-2062 prepared by Bio Dynamics, Inc. EPA Accession. No. 247617 - 247621. MRID No. 00093879.

A. Experimental Design

Groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at concentrations of 0, 30, 100 or 300 ppm for 26 months. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained.

B. Survival Analysis

There were no treatment-related effects on survival at any dose level.

C. Discussion of Tumor Data

There was an increase in the incidences of interstitial cell tumors in the testes of male rats at the low (3/5; 6%), mid (1/50; 2%) and the high dose (6/50; 12%; p=0.013) when compared to controls (0/50; 0%). In 1991, HED's Cancer Peer Review Committee (CPRC) did not consider the increases to be treatment-related based on the following weight of evidence considerations: 1) lack of dose-response; 2) absence of preneoplastic lesions (*i.e*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5; range, 3.4% to 6.7%;) and 5) no interstitial cell tumors were seen when tested at much higher doses in the same strain of rats in an another study (discussed below).

Although there was no evidence of a treatment-related increase in the incidences of pancreatic islet cell tumors in male rats, the data are presented in Table 4 since this tumor also seen in the second study discussed below.

Table 4. Pancreatic Islet Cell Tumors in Male Sprague Dawley Rats (MRID 00093879)

Tumor Type	0 ppm	30 ppm	100 ppm	300 ppm
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Combined (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

C. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The CARC conclude that the highest dose tested was not adequate to assess the carcinogenic potential of glyphosate. Consequently, a second study was conducted (discussed below)

2. Stout, L. D. and Ruecker, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September, 26, 1990, MRID No. 4143801; Historical Controls; MRID No. 41728700.

A. Experimental Design

Groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary concentrations of 0, 2000, 8000 or 20,000 ppm 24 months. These concentrations were equivalent to 0, 100, 400 or 1000 mg/kg/day (Limit Dose), respectively. An interim sacrifice was conducted on 10 rats/sex/dose at 12 months.

B. Discussion of Tumor Data

There was no evidence of a treatment-related carcinogenic response in either sex. Most frequently seen tumors were pancreatic cell adenomas in males are presented in Table 5 and the historical control data in Table 6. Hepatocellular adenomas seen in males are presented in Table 7 and the historical control data in Table 8. The thyroid C-cell adenomas and/or carcinomas observed in males and females are presented in Tables 9 and 10, respective, and the historical control data in Table 11.

(i) Pancreas

There was no dose-response for the statistical significance; increases at the low and high dose groups but not at the mid-dose group.

Table 5. Pancreatic Islet Cell Tumors in Male Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 4143801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20,000 ppm
Adenomas	1/43[a]	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
P =	0.170	0.018*	0.135	0.042*
Carcinomas	1/43[c]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p =	0.159	0.409	0.467	0.472
Combined	2/43	8/45	5/49	7/48
(%)	(2)	(18)	(10)	(15)
p =	0.241	0.052	0.275	0.108

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 81 in the 20,000 ppm group

c. First carcinoma observed at week 105 in the controls (0 ppm)
* Significant in a pair-wise comparison ($p<0.05$)

Historical control data on the incidence of pancreatic islet cell adenomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory) are presented in Table 6.

Table 6. Historical Control Data – Pancreatic islet cell Adenomas in Male Sprague Dawley Rats (MRID No. 41728700)

Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59
%	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%

The CPRC concluded that the pancreatic islet cell adenomas are not treatment-related based on the following weight of evidence considerations: 1) although the incidences at the low (18%) and high (15%) dose groups exceeded the historical control range (1.8-8.5%), the lack of statistically significance in the Peto trend test; 2) the tumor incidence in the concurrent control was at the low end of the historical control range; 3) considerable inter-group variability in the numbers of males with tumors (i.e, no dose-response); and the absence of preneoplastic changes virtually precludes this being a carcinogenic effect); 4) there was no progression from adenomas to carcinomas; and 5) the apparent statistical significance of the pairwise comparisons of the treated groups with the concurrent control is attributable to the low incidences in the controls and not to an actual carcinogenic response. Furthermore, the incidences of pancreatic cell tumors for the two studies (doses ranging from 3 to 1000 mg/kg/day) did not show a dose-dependent increase for adenomas or the combined (adenomas/carcinomas) and the incidences were within the historical control range (0 to 17%) reported in the open literature (Arnold *et al.,* 1985; Borelli *et al*, 1990; Borrelleca *et al*, 1986, 1989, 1990; Burnett *et al*, 1988; Trochimowicz *et al*, 1988; Truhault *et al*., 1989: Wischke *et al*., 1988; Quast *et al*., 1986).

(ii) Liver

There was no statistically significant (trend or pairwise) increases in the occurrence of benign or malignant tumor type (Table 7). The observed variations did not show a dos relationship, and were within the range of the historical control data.

Table 7. Glyphosate: Hepatocellular Tumors in Male Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 4143801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20,000 ppm
Adenomas (%) P =	2/44[a] (5) 0.016	2/45 (4) 0.683	3/49 (6) 0.551	7/48[b] (15) 0.101
Carcinomas (%) p =	3/44 (7) 0.324	2/45 (4) 0.489	1/49 (2) 0.269	2/48[c] (4) 0.458
Adenoma/Carcinoma (%) p =	5/44 (11) 0.073	4/45 (9) 0.486	4/49 (8) 0.431	9/48 (19) 0.245

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 88 in the 20,000 ppm group
c. First carcinoma observed at week 85 in the 20,000 ppm group

Historical control data on the incidence of hepatocellular adenomas and carcinomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory) are presented in Table 8.

Table 8. Historical Control Data – Pancreatic islet cell Adenomas in Male Sprague Dawley Rats (MRID No. 41728700)							
Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Adenomas	5/60 (8.3%)	11/68 16.2%)	1/70 (1.4%)	3/59 (5.1%)	11/60 (18.3%)	5/60 8.3%)	4/60 (6.7%)
Carcinomas	4/60 (6.7%)	0/68 (0%)	1/70 (1.4%)	2/59 (3.4%)	3/60 (5%)	1/60 (1.7%)	0/60 (0%)

The CPRC concluded that the slightly increased incidence of adenomas in male rats are not treatment related since: 1) the increase was not statistically significant in pair wise comparison with the controls; 2) the incidences were within the historical control range; 4) except for a single animal at the mid dose at late in the study (89 weeks), no hyperplasia (*i.e*, preneoplastic changes) was seen; and 5) there was no progression from adenomas to carcinomas.

(iii) Thyroid

The increases in C-cell adenomas observed at the mid and high dose group rats of both

sexes were did not show statistically significant in pairwise comparisons with the controls Table 9 and 10, respectively. Historical control data are presented in Table 11.

Table 9. Glyphosate: Thyroid C-Cell Tumors in Male Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 4143801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20,000 ppm
Adenomas (%) P =	2/54[a, b] (4) 0.069	4/55 (7) 0.348	8/58 (14) 0.060	7/58 (12) 0.099
Carcinomas (%) p =	0/54 (0) 0.452	2/55[c] (4) 0.252	0/58 (0) 1.000	1/58 (4) 0.518
Adenoma/Carcinoma (%) p =	2/54 (11) 0.077	6/55 (11) 0.141	8/58 (14) 0.060	8/58 (14) 0.060

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 54 in the controls
c. First carcinoma observed at week 93 in the 20,000 ppm

Table 10. Glyphosate: Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 4143801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20,000 ppm
Adenomas (%) P =	2/57[a] (4) 0.031	2/60 (7) 0.671	6/59[b] (10) 0.147	6/55 (11) 0.124
Carcinomas (%) p =	0/57 (0) 0.445	0/60 (0) 1.000	1/59[c] (2) 0.509	0/55 (0) 1.000
Adenoma/Carcinoma (%) p =	2/57 (4) 0.033	2/60 (3) 0.671	7/59 (12) 0.090	6/55 (11) 0.124

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 72 in the controls
c. First carcinoma observed at week 93 in the 8000 ppm group.

Table 11. Historical Control Data – Thyroid C-cell Tumors in Sprague Dawley Rats (MRID No. 41728700)		
Tumor Type	Males	Females
Adenomas	1.8 – 10.6%	3.3 – 10.0%
Carcinomas	0.0 – 5.2%	0.0 – 2.9%

The CPRC concluded that the thyroid tumors in either sex are not treatment-related since: 1) the increased incidences exhibited no statistically significant trend or in pairwise comparisons with the controls in males; 2) in females, there was only a trend but no pairwise significance; 3) there was no progression from adenomas to carcinomas; and 4) there was no dose-related increase in severity of grade or incidence of hyperplasia in males or females.

C. Non-Neoplastic Lesions

There were no treatment-related precursor lesions at any dose level.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was the limit dose.

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3. Atkinson, C., Strutt, A., Henderson, W., et al. (1993). 104-Week chronic feeding/ oncogenicity study in rats with 52-week interim kill. Inveresk Research International (IRI), Tranent, Scotland. Study No. 438623; IRI Report No. 7867. April 7, 1993. MRID No. 49631701. Unpublished.

A. Experimental Design

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 Sprague-Dawley rats/sex/dose in the diet at 0, 10, 100, 300, and 1000 mg/kg bw/day to both sexes for 104 weeks. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of treatment.

B. Discussion of Tumor Data

There were no treatment-related increases in the occurrence of any tumor type in this study.

C. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was the limit dose and at this dose increased salivary gland weight accompanied by cellular alterations in the mandibular and/or parotid glands occurred in both males and females.

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4. Syngenta. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta. (MRID No. 49631701),

A. Experimental Design

In a combined chronic toxicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 male and 52 female rats received diets containing 0, 2,000, 6,000, and 20,000 ppm glyphosate for 24 months. The achieved doses were 0, 121, 361 or 1214 mg/kg/day in males and 0, 145,437 or 1498 mg/kg/day in females, respectively. Three satellite groups of 12 rats/sex/group were also included for interim sacrifice at 12 months of treatment to study non-neoplastic histopathological changes. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

B. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

C. Discussion of Tumor Data

The increase in the incidence of hepatocellular adenomas in male rats (5/52; 10%) at the high dose (1214 mg/kg/day) when compared to control (0/52) was not considered to be treatment-related due to 1) absence of statistical significance in a pair-wise test; 2) absence of dose-response relationship; 3) lack of progression to malignancy; 4) no evidence of liver damage or pre-neoplastic lesions; and 5) the incidences were within the range (0-11.5%) of historical controls in 26 studies conducted during the relevant time period (1984-2003) at the testing laboratory.

D. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested.

E. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested exceed the limit dose in both sexes (1214 mg/kg/day in males and 1498 mg/kg/day in females). Treatment-related findings at these doses were observed in the liver and kidney, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, hematuria and slight increases in the proliferative cholangitis and hepatitis.

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5. Feinchemie Schwebda. (1996). Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Bangalore, India: Rallis India, Ltd. (Cited in Greim et al, 2015).

A. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (986.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 100, 1000, and 10,000 ppm glyphosate for 24 months. The average achieved doses were 0, 7.4, 73.9, and 740.6 mg/kg/day. In addition, one vehicle control with 10/sex, and a second10, 000 ppm high dose group with 20 rats/sex/ group included for interim sacrifice after one year of treatment, to study non-neoplastic histopathological changes. Parameters evaluated included clinical signs, body weights, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy, and histopathological examination.

B. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

C. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study (Attachment 1).

D. Non-Neoplastic Lesions

There were no non-neoplastic lesions at any dose level in either sex.

E. Adequacy of Dosing for Assessment of Carcinogenicity

The doses tested were determined to be adequate in both sexes since the highest dose tested (741 mg/kg/day) approached the limit dose (1000 mg/kg/day).

6. Arysta Life Sciences. (1997a). HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim et al, 2015).

A. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (94.6-97.6% pure) was administered to groups of Sprague-Dawley rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 3,000, 10,000, or 30,000 ppm glyphosate for 24 months. The achieved doses were 0, 104, 354 or 1127 mg/kg/day in males and 0, 115, 393, or 1247 mg/kg/day in females, respectively. Satellite groups of 30 rats/sex/group were also included for interim sacrifice at 26, 52 and 78 weeks, to study non-neoplastic histopathological changes. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

B. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

C. Discussion of Tumor Data

There were no treatment-related increases in the occurrence of any tumor type in this study (Attachment 2).

D. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

E. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose 10,000 ppm (345/393 mg/kg/day) was the limit dose and there were increased cecum weights, distension of the cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, and decreased body weights.

7. Nufarm. (2009a). Glyphosate Technical: Dietary Combined Chronic Toxicity/ Carcinogenicity in the Rat. Shardlow, Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim et al, 2015).

A. Experimental Design

In a combined chronic toxicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 1500, 5000, and 15000 ppm glyphosate for 24 months. To ensure that a received limit dose of 1000 mg/kg/day was achieved, the highest dose level was progressively increased to 24,000 ppm. The achieved doses were 0, 86, 285 or 1077 mg/kg/day in males and 0, 105, 349 or 1382 mg/kg/day, in females. Three satellite groups of 12 rats/sex/group were also included for interim sacrifice at 12 months of treatment, to study non-neoplastic histopathological changes. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

B. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested.

C. Discussion of Tumor Data

There were no treatment-related increases in any tumor type in this study (Attachment 3).

D. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in either sex at any dose level.

E. Adequacy of Dosing for Assessment of Carcinogenicity

In both sexes, the highest doses tested was the limit dose.

B. Studies in Mice

8. Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamic Inc., dated July 21, 1983. Report No. 77-2011. EPA Accession No. 251007 -251009, and 251014.

A. Experimental Design

In a carcinogenicity study, groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary levels of 0, 1000, 5000, or 30,000 ppm for two years. The mean achieved doses were 0, 157, 814 or 4841 mg/kg/day in males and 0, 190, 955 or 5874 mg/kg /day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, necropsy and histopathological examination.

B. Discussion of Tumor Data

The incidences of renal tubule adenomas were as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose and 5/50 at the high dose (TXR No. 004370).

In 1985, the Registrant directed a re-evaluation of the original renal section by a consulting pathologist (Dr. Kuschner). This evaluation identified a small renal tubule adenoma in one control male (animal number 1028) mouse which was not diagnosed as such in the original pathology report (TXR No. 004855).

In 1986, at the request of the agency, additional renal sections (3 sections/ kidney/ mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice was not compound-related (TXR No. 00590).

At the request of the agency, the Pathology Work Group (PWG) examined the all sections of the kidneys including the additional renal sections. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 12. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular-cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparisons of treated groups with the controls and there was no evidence of a significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound related nephrotoxic lesions, including preneoplastic changes, were not present in this study (TXR No. 005590).

Table 12. Glyphosate: Kidney Tumor in Male CD-1 Mice				
Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
	0 mg/kg/day	157 mg/kg/day	814 mg/kg/day	4841 mg/kg/day
Tubular-cell adenoma	1/49	0/50	0/50	1/50
Tubular-cell carcinoma	0	0/50	1/50	2/50
Combined incidence	1/49 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)

Historical control data from the testing laboratory (Bio-dynamics) during the glyphosate-study period (1976-1982) are presented in Table 13.

Table 13. Historical Control Data- Kidney tumors in CD-1 Mice – Bi/dynamics Inc.														
Study I.D	A		B		C		D		E		F		G	
Study Period	6/78 - 7/80		12/77- 4/80		12/77- 3/80		10/78- 4/81		11/78- 4/81		11/77- 4/80		10/77-4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma		1								2				

Historical control data from 14 studies conducted between 1977 and 1981 at the testing laboratory indicated that the mouse renal tumors ranged from 0 to 3.3% and the incidence in the current study (3/50; 6%) exceeded the upper limit of the historical control range (TXR No. 007252).

The CPRC classified glyphosate as a Group E chemical; Evidence of Non Carcinogenicity in Humans based on lack of convincing evidence for carcinogenicity in adequate studies in two animal species, there was no evidence of genotoxicity, and lack of structure activity concerns. The CPRC based this classification on the following weight-of-evidence considerations (TXR No. 008898):

- For the pancreatic islet tumors: a) there was no statistically significant positive dose-related trend in the occurrence of these tumors or in the incidence of hyperplasia in males over the wide range of dosing (2000 to 20,000 ppm), and b) there was no progression to carcinoma. The incidence of pancreatic islet cell tumors for the two rat studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range (0 to 17%) of open literature control data for male Sprague-Dawley rats. No increased incidence of these tumors was observed in female rats in comparison to control rats.

- For the C-cell thyroid tumors, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence c-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose- related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the c-cell adenomas in males and females are not considered compound-related.

- For the hepatocellular adenomas in male rats, the incidence was within the range of historical controls from Monsanto's EHL. This increase was not significant in the pair-wise comparison with controls and there was no progression from adenoma to carcinoma. The incidence of hyperplasia was not compound-related. There were no dose- related increases in the incidences of other hepatocellular lesions. Therefore, the increased incidence of hepatocellular adenomas in males was not considered compound-related.

- Glyphosate produced an equivocal carcinogenic response in male mice characterized by an incidence of renal tubular neoplasms. The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not feel that this lesion was compound-related.

C. Non-Neoplastic Lesions

Dose-depended non-neoplastic lesions seen in both sexes at the high dose (30,000 ppm) included increased hepatocyte hypertrophy, hepatocyte necrosis and interstitial nephritis in males and an increased incidence of proximal tubule epithelial basophilia and hypertrophy in female mice.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose tested in males (4841 mg/kg/day) and females (5874 mg/kg/day) was approximately 4 to 5-fold higher than the limit dose (1000 mg/kg/day), which produced highly significant reduction in body weights in both sexes. Therefore, the doses tested were determined to be adequate to assess the carcinogenic potential of glyphosate in this study.

9. **Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International,**

Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702.

A. Experimental Design

In a carcinogenicity study, glyphosate (97.5 – 100.2% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. No interim sacrifices were done. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, necropsy and histopathological examination.

B. Discussion of Tumor Data

Table 14. Hemangiosarcomas in Male CD-1 Mice Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcomas	0/47[a]	0/46	0/50	4/45
(%)	(0)	(0)	(0)	(9)
P =	0.00296**	1.00000	1.00000	0.05332

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
Note: ** Significance of trend ($p<0.01$) denoted at control.

Hemangiosarcomas was found in 4/45 (9%) high-dose male mice compared to none in the controls. In the treated mice at the high dose, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. All were classified as malignant. No hemangiosarcomas was found in the control or low- and mid-dose mice.

In females, hemangiosarcomas were found in 2 of 50 (4%) mice at the low-dose (one with the tumor in the uterus and the other in the spleen only) and in 1 of 50 (2%) at the high dose (hemangiosarcomas in the liver only). All were considered malignant. No hemangiosarcomas was found in the control and mid-dose female mice.

The increase in male mice was not considered to be treatment-related due to 1) absence of statistical significance in the pair wise analysis; 2) lack of dose-response relationship; 3) the incidences was near or the same as the upper limit (0-8%) for the performing laboratory; no evidence of pre-neoplastic lesions; 4) hemangiosarcomas were not seen in the other four studies when tested at comparable doses (946-1467 mg/kg/day) or at considerably higher doses (4348-5874 mg/kg/day) in this strain of mice; and 4) the considerable inter-group variability in the number of female mice with this tumor.

C. Non-Neoplastic Lesions

No treatment-related effects were noted in the spleen of male and female mice. There was a slight, but statistically significant increase in mineral deposits in the brain in mid- and high-dose male mice (4/49, 4/24, 7*/21, and 13*/50 in control, low-dose, mid-dose, and high-dose, * = $p \leq 0.05$, respectively). Smaller non-significant increases were observed in female mice (4/50, 4/33, 5/24 and 8/50). Kidney cysts were statistically increased in low- and mid-dose male mice (11/50, 21*/50, 22*/50, and 15/50 in control, low-dose, mid-dose, and high-dose, * = $p \leq 0.05$, respectively). No increase of kidney cysts was found in female mice. All other lesions were commonly seen this age and strain of mouse.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose tested was the limit dose (1000 mg/kg/day).

10. Arysta Life Sciences. (1997b). HR-001: 18-Month Oncogenicity Study in Mice. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015).

A. Experimental Design

In a carcinogenicity study, groups of ICR-CD-1 mice (50/sex/group received diets containing glyphosate (94.6-97.6% pure) at 0, 1600, 8000 or 40,000 ppm for 18 months. The achieved doses were 0, 165, 838 or 4348 mg/kg/day in males and 0, 153,787 or 4116 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

B. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

C. Discussion of Tumor Data

No statistically significant increase in any tumor type was seen (Attachment 4).

D. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

E. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes exceeded (4-fold) the limit dose (1000 mg/kg/day).

11. Feinchemie Schwebda. (2001). Carcinogenicity Study with Glyphosate Technical in Swiss Albino Mice. Bangalore, India: Rallis India, Ltd. (Cited in Greim *et al.*, 2015)

A. Experimental Design

In another carcinogenicity study with Swiss mice (50/sex/dose), glyphosate (> 95% pure) was administered in the diet at concentrations of 0, 100, 1000 or 10, 000 ppm for 18 months. These concentrations corresponded to 0, 14.5, 150 or 1454 mg/kg/day in males and 0, 15, 151 or 1467 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

B. Survival Analysis

There was increased mortality in both sexes at the high dose; a viral infection within the colony was reported.

C. Discussion of Tumor Data

There were statistically significant increases ($p < 0.05$) in the incidence of malignant lymphomas at the high dose in both sexes. The incidences in the treated males (19/50; 38%) compared to controls (10/50; 20%). The incidences in females were (25/50; 50%) when compared to controls (18/50; 36%). The incidences in both sexes were at the higher end of the historical control mean and range of the testing laboratory: males, 18.4%; range, 6-30% and females, 39.6%; range, 15-58%) (Attachment 5).

These were not considered to be treatment-related since: 1) lack of corroborative pre-neoplastic lesions; 2) lymphomas are the most common spontaneously occurring tumors in mice; 3) this finding was not replicated in the same strain of mice in the other four studies either at a similar dose (1000 mg/kg/day; Atkins *et al.*, ,1993 and Nufarm, 2009) or at doses 4 to 5-fold higher (438 mg/kg/day, Arysta, 1997 and 5874 mg/kg/day, Hogan *et al.,* 1983); 4) the incidences in the current study were within the normal variation of background occurrence; and 5) the uncertainty as to whether or not the viral infection present in the animal colony may have played contributed to this finding.

D. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

E. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes exceeded the limit dose (1000 mg/kg/day)

12. Nufarm. (2009b). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015)

A. Experimental Design

In another feeding study, CD-1 mice (50/sex/dose) received glyphosate (94.6-97.6%, pure) at 0, 500, 1500, or 5000 ppm for 18 months. The calculated test substance intake was 0, 85, 267 or 946 mg/kg/day. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

B. Discussion of Tumor Data

There were no statistically significant increase in any tumor type (Attachment 6).

C. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose tested approached the limit dose (1000 mg/kg/day)

C. Discussion

The carcinogenic potential of glyphosate has been evaluated in seven studies in Sprague-Dawley or Wistar rats and five studies in CD-1 mice. These studies and their results have been evaluated by a number of regulatory (USEPA) and international scientific organization (JMPR, IARC).

Each of these groups have concluded that glyphosate is not carcinogenic following dietary administration at doses ranging from 3.0 to 1500 mg/kg/day for 2 years to male and female Sprague –Dawley or Wistar rats or at doses ranging from 15.0 or 5864 mg/kg/day for 18 months to male and female CD-1 mice (USEPA, 1993; JMPR, 2004).

In 2015, the IARC, determined that there is "sufficient evidence of carcinogenicity in experimental animals" for glyphosate. This conclusion was based on the positive trend for renal tubular carcinoma observed in male mice in one study (MRID No. 25100704) and on presence of statistically significant increase in hemangiosarcomas in male mice, and a non-statistically significant increase in the incidence of histiocytic sarcoma in the lymphoreticular/hematopoietic tissue in males and females in the other study (MRID No. 49631702).

The USEPA did not consider the renal tubular tumors observed in male mice in the same study evaluated by IARC (MRID No. 25100704) to be treatment-related based on the following weight-of-evidence considerations: 1) the increase at the high dose (3/50; 6%) was minimal compared to the controls (1/49; 2%) considering that the high dose (4800 mg/kg/day) was approximately 5-fold higher than the limit dose; 2) the increased was not statistically significant in pairwise comparison with concurrent controls; 3) there was no evidence of kidney damage; 4) lack of pre-cursor lesions (e.g. tubular necrosis/ regeneration, hyperplasia, hypertrophy etc); and 5) the additional examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well. This conclusion was supported by the agency's FIFRA SAP which concluded that the evidence for renal tumors were equivocal, was mainly driven by adenomas and although the incidences was slightly exceeded the historical control, there was no statistically significant pairwise difference when compared to the controls. It is also noted that kidney tumors were not replicated in the other four studies when tested at doses ranging from 85 to 5874 mg/kg/day in this strain of mice as discussed above.

The USEPA did not consider the hemangiosarcomas and the lymphoreticular/ hematopoietic tumors observed in male mice evaluated by IARC to be treatment-related based on the following considerations: 1) absence of statistical significance in the pair wise analysis; 2) lack of dose-response relationship; 3) the incidences was near or the same as the upper limit (0-8%) for the performing laboratory; no evidence of pre-neoplastic lesions; 4) hemangiosarcomas were not seen in the other four studies when tested at comparable doses or at significantly higher doses (4000-5000 mg/kg/day) in this strain of mice; 4) the considerable inter-group variability in the number of male and female mice with lymphoreticular/hematopoietic tumors.

The IARC identifies a cancer "hazard" if an agent (i.e., chemical) is capable of causing cancer under some circumstances and the agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The IARC also considers that there is "*sufficient evidence of carcinogenicity"* based on the occurrence of increased tumors (benign, malignant, or combination) in: 1) two or more species of animals; 2) two or more independent studies in on species; and 3) an increased incidence of tumors in both sexes of a single species. Furthermore, a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites (IARC Preamble, 2006).

In accordance with its Preamble, the IARC made the determination that the presence of kidney tumors in one study and hemangiosarcomas in the other study satisfied the "Preamble criteria" for the occurrence of tumors in "two or more independent studies in one species" and thus the classification of "sufficient evidence for carcinogenicity". They did not consider the following: there was no pair-wise significance when compared to controls; lack of non-neoplastic renal tubular lesions; nor progression to malignancy; and examination of multiple sections of kidneys from all groups resulted in no additional neoplasms.

In contrast, the USEPA's carcinogenicity classification is based on a weight-of-evidence considerations in accordance with the agency's 2005 Guideline for Carcinogen Risk Assessment. Conclusions are based on the combined strength and coherence of inferences appropriately drawn from all of the available information. The following observations add significance to the tumor findings: tumors in multiple species, strains or both sexes; dose-related increases; progression of lesions from preneoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and evaluation of tumor effects takes into consideration both biological and statistical significance of the findings Significance is generally increased by the observation of more of these factors. For a factor such as malignancy, the severity of the observed pathology can also affect the significance.

IV. TOXICOLOGY

1. Metabolism

Two metabolism studies with rats are available. In the first study, single or repeated doses of radiolabeled 4C-glyphosate were administered orally to male and female Sprague-Dawley rats. Following a single oral dose of, 4C-glyphosate, 30 to 36% of the dose was absorbed and less than 0.27% of the dose was eliminated as CO2• Ninety-seven point five percent of the administered dose was excreted in the urine and feces as the parent compound, glyphosate. Amino methyl phosphonic acid (AMPA) was the only metabolite found in urine (0.2-0.3% of the administered dose) and feces (0.2-0.4% of the administered dose). Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in bone tissue. Repeated dosing at 10 mg/kg did not significantly change the metabolism, distribution or excretion of glyphosate.

In a second study (M), male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled 14C-glyphosate. The dose level of glyphosate used for male and female rats was 1150 mg/kg. Blood sample13 were collected 0.25, 0.50, 1, 2, 4, 6 and 10 hours after injection. Femoral bone marrow samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after injection. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.0044% and 0.0072%, respectively, of the administered dose. Assuming first order kinetics, the decrease in radioactivity in bone marrow occurred with a half-life of 7.6 and 4.2 hours for males and females, respectively. Similarly, the half-lives of the radioactivity in plasma were approximately 1 hour for both sexes. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow and that it is even more rapidly eliminated from plasma.

2. Mutagenicity:

In 1991, the Carcinogenicity Peer Review Committee concluded that there was no evidence of genotoxicity for glyphosate based on negative findings in submitted guideline studies for the bacterial reverse mutation test (MRID 00078620), *in vitro* mammalian cell gene mutation test in CHO cells (MRID 00215737), *in vivo* mammalian erythrocyte micronucleus test (MRID 0025137) and in a "rec assay" used to detect DNA damaging agents in *Bacillus subtilis* (MRID 00078619) (TXR# 0008898). Glyphosate was also negative in two unacceptable studies evaluating DNA repair in rat hepatocytes (MRID 00075619) and dominant lethal mutations in mice (MRID ??).

Glyphosate has also been evaluated for its genotoxic potential in other regulatory and published literature studies. Extensive reviews of the available genotoxicity studies for glyphosate and glyphosate products were conducted by Williams *et al.* (2000) and by Kier and Kirkland (2013). IARC also conducted a review of the publically available genetic toxicity data for glyphosate and glyphosate-based formulations (IARC Monograph, 2015).

Williams *et al.*, (2000) concluded that "glyphosate is neither mutagenic nor clastogenic." Similarly, Kier and Kirkland concluded a "lack of genotoxic potential for both glyphosate and glyphosate based formulations (GBFs) in core gene mutation and chromosomal effect endpoints." Kier and Kirkland (2013) also stated that "the observations of DNA damage effects seems likely to be secondary to cytotoxic effects". However, IARC (2015) concluded that "there is strong evidence that glyphosate cause's genotoxicity". It should be noted that the IARC's conclusion was based not only on studies conducted with the active ingredient but also on studies conducted with the formulation products such as Roundup. Round up is a combination of the active ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) which enhances the spreading of spry droplets when contact foliage. Also, review article by Kier and Kirkland and supplemental information provided on the publisher's website were not considered in the IARC evaluation.

In this assessment, the CARC considered the studies submitted to the Agency under 40 CFR Part 158 as well as the studies presented in the review articles by Williams *et al.* (2000), Kier and Kirkland (2013) and the IARC monograph (2015). Consistent with OPP's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf), literature studies discussed in the reviews such as IARC that did not meet the Klimisch criteria for reliability (*e.g.* lack of inadequate glyphosate purity information or the test material) were not considered by CARC. CARC determined the mutagenic potential of glyphosate in humans by conducting a weight of evidence evaluation of the results from the cited bacterial reversion (Ames) assays, *in vitro* mammalian gene mutation assays, *in vitro* and *in vivo* chromosomal aberration and micronucleus assays as well as other relevant assays evaluating DNA damage.

a. Bacterial reverse mutation assays

As shown in Table 15, glyphosate was not mutagenic in any of the *in vitro* bacterial mutation assays using *S. typhimurium* or *E. coli* tester strains with or without microsomal S9 metabolic activation. These results are consistent with the negative findings in the previously reviewed EPA guideline (870.5100) bacterial reverse gene mutation study (MRID 00078620).

Table 15 Results from Bacterial Reverse Gene Mutation Assays[1]

Author	Cell/Strain[2]	Purity	Highest test concentration	Results –S9	Results +S9
Akanuma, M. (1995)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.7%[3]	5000 µg/plate	Negative	Negative
Callander, R.D. (1996)	TA98, TA100, TA1535, TA1537; WP2P and WP2*uvr*A	95.6%[3]	5000 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	76.1%[4]	100 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	96.4%	3160 µg/plate	Negative	Negative
Flügge, C. (2009)	TA98, TA100, TA102, TA1535, TA1537	98.8%	3160 µg/plate	Negative	Negative
Jensen, J.C. (1991)	TA98, TA100, TA1535, TA1537	98.6%	2500 µg /plate w/o S9; 5000 µg /plate w/ S9	Negative	Negative
Li and Long (1998)	TA98, TA100, TA1535, TA1537, TA1538;	98%	5000 µg/plate	Negative	Negative
NTP (1992)	TA97, TA100, TA1535	98%	10,000 µg /plate	Negative	Negative
Schreib, G. (2010)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96%	5000 µg/plate	Negative	Negative
Shirasu et al. (1978)	TA98, TA100, TA1535, TA1537, TA1538 and WP2*uvr*A	98.4%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007c)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.0%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007a)	TA98, TA100, TA1535, TA1537; WP2uvrA	95.1%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009b)	TA98, TA100, TA1535, TA1537;WP2P and WP2*uvr*A	96.3%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009a)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96.66%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007b)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	97.7%	5000 µg/plate	Negative	Negative
Suresh, T.P. (1993)	TA98, TA100, TA1535, TA1537, TA1538	96.0%	1000 µg/plate	Negative	Negative
Thompson,	TA98, TA100, TA1535,	95.3%	5000 µg/plate	Negative	Negative

1. Studies cited in Williams et al. (2000), and Kier

P.W. (1996)	TA1537; WP2*uvr*A				

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.
2. *Salmonella typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and/or TA1538) or *E. coli* strains (WP2P and WP2*uvr*A)
3. Glyphosate acid
4. Monoammonium glyphosate salt

b. *In vitro* mammalian cell gene mutation assays

Glyphosate did not induce forward mutations in mouse lymphomas cells or Chinese hamster ovary (CHO) cells in the presence or absence of metabolic (S9) activation (Table 16).

Table 16. Results from mammalian gene mutation assays[1].

Author	Assay Type	Cell type	Purity	Highest conc.	Result -S9	Result +S9
Clay (1996)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	95.6%	1.0 mg/mL	Negative	Negative
Jensen, J.C. (1991)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	98.6%	5.0 mg/mL	Negative	Negative
Li and Long (1988)	*In vitro* mammalian gene mutation	CHO cells/ HGPRT locus	98%	22.5 mg/mL	Negative	Negative

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.

c. *In vitro* chromosomal aberration assays

Lioi *et al*., reported positive findings for chromosomal aberrations in human and bovine lymphocytes treated with glyphosate *in vitro* in the absence of S9 activity. However, Van de Waart reported no significant increase in chromosomal aberrations in human lymphocyte treated with up to 0.56 mg/mL (-S9) and 0.33 mg/mL (+S9) glyphosate, an approximately 70-fold higher concentration than where Lioi *et al*. reported aberrations. Glyphosate was negative in two other *in vitro* chromosomal aberrations studies in human lymphocytes (Fox, 1998 and Manas, 2009) and did not induce chromosomal aberrations in Chinese hamster lung cells (Matsumoto, 1995 and Wright 1996). A summary of the findings is presented in Table 17.

Table 17. Results from *in vitro* chromosomal aberration assays[1].

Authors	Assay	Cell type	Purity	Highest test concentration	Result -S9	Result +S9
Van de Waart (1995)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	0.56 mg/mL with S9; 0.33 mg/mL w/o S9	Negative	Negative
Fox, V. (1998)	Chromosome Aberration	Human peripheral lymphocytes	95.6%[2]	1250 ug/mL	Negative	Negative
Lioi et al. (1998a)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	1.4 mg/L	Positive	Not Tested

Manas et al. (2009)	Chromosomal Aberration	Human peripheral lymphocytes	96%	6 mM	Negative	Not Tested
Lioi et al. (1998b)	Chromosomal Aberration	Bovine peripheral lymphocytes	>98%	2.9 mg/L	Positive	Not Tested
Matsumoto, K. (1995)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.68%[2]	1000 ug/mL	Negative	Negative
Wright, N.P. (1996)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.3%	1250 ug/mL	Negative	Negative

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

d. *In vivo* micronucleus and chromosomal aberration assays

Numerous studies were evaluated to determine the potential for glyphosate to induce micronuclei in rodent bone marrow cells. Studies included both intraperitoneal (IP) and oral routes of glyphosate administration. In a literature study by Bolognesi *et a*l. (1997), the authors reported an induction of micronuclei in male mice treated with up to 300 mg/kg (injected as two ½ doses). It is noted that this study included only 3 animals/dose; rather than the 5 animals/dose recommended in the agency's test guideline (870.5395). In another literature study, Manas *et a*l. (2009) reported an induction of micronuclei in BALB/C mice when tested up to 200 mg/kg glyphosate. Additionally, Suresh *et al*. (1993) reported an increase in micronuclei in females only in Swiss albino mice treated with 5 mg/kg glyphosate; a dose that is more than twice the limit dose for the agency's guideline study. Although the above authors reported positive findings, a vast majority of the *in vivo* genotoxicity studies (including the previously reviewed guideline mammalian micronucleus test) were negative at doses similar to or higher than the studies discussed above, regardless of the dosing regimen or route of administration. A summary of the findings are reported in Table 18.

Table 18. Results from *in vivo* genotoxicity assays[1].

Author	Assay Type	Species/strain	Purity	Highest conc.	Results	Comments
Bolognesi *et al.* (1997)	Micronucleus test	Male mice (strain not provided)	99.9%	300 mg/kg	Positive	Two IP injections of ½ dose; 3 mice/dose
Durward, R. (2006)	Micronucleus test	Young adult male and female albino Crl:CD	95.7%	600 mg/kg	Negative	Single IP injection; Significant increase in % PCEs per 1000 erythrocytes was observed in the 24-

		- 1TM(ICR)BR mice				hour; however not 48 - hour at 600 mg/kg
Flügge, C. (2009)	Micronucleus test	Male and female CD rats	98.8%	2000 mg/kg	Negative	Single dose; oral gavage
Fox and Mackay (1996)	Micronucleus test	Male and female CD-1 BR mice	95.6%[2]	5000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2005)	Micronucleus test	Male and female NMRI mice	97.73 %	2000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2008)	Micronucleus test	NMRI male mice	99.1%	2000 mg/kg	Negative	Single dose; oral gavage
Jensen, J.C. (1991)	Micronucleus test	Young adult male and female NMRI SPF mice	98.6%	5000 mg/kg	Negative	Single dose; oral gavage
Manas et al. (2009)	Micronucleus	BALB/C mice	96%	200 mg/kg	Positive	Two IP doses, 1 day apart
NTP (1992)	Micronucleus test	Male and female B6C3F1 mice	99%	11,379 mg/kg/day	Negative	Dietary admin., 13 weeks
Suresh, T.P. (1993)	Micronucleus test	Young Swiss albino male and female mice	98.6%	5000 mg/kg	Males: Negative. Females: Positive	Two doses 1 day apart; oral gavage
Suresh, T.P. (1994)	Mouse Bone Marrow Chromosome Aberration	Male and female Swiss albino mice	96.8%	5000 mg/kg	Negative	Two doses, 24 hours apart; oral gavage

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. IP= intraperitoneal injection

e. Other genotoxicity assays

Inconsistent responses were reported in number of assays designed to detect DNA damage, including sister chromatid exchange (SCE) assay, unscheduled DNA synthesis assay, and the comet assay (also known as the single cell electrophoresis assay). Positive responses in these assays do not necessarily indicate a chemical is DNA-reactive (*i.e*. mutagenic), but rather under conditions of the assay, DNA damage occurred. Glyphosate was negative in two rodent dominant lethal test and in two Rec- DNA repair tests in *B. subtilis*. The results of these genotoxicity studies are presented in Table 19.

Table 19. Additional genotoxicity assays

Authors	Assay Type	Cell Type	Purity	Highest test	Results

				conc.	
Bolognesi et al. (1997)	Sister chromatid exchange (SCE)	Human Peripheral blood (in vitro)	99.9%	1000 ug/mL	Positive
Lioi et al. (1998a)	SCE	Human Peripheral blood (in vitro)	>98%	1.4 mg/L	Equivocal
Lioi et al. (1998b)	SCE	Bovine Peripheral blood (in vitro)	>98%	2.9 mg/L	Equivocal
Li and Long (1988)	Unscheduled DNA synthesis (UDS)	Rat hepatocytes (in vitro exposure)	98%	0.125 mg/mL	Negative
Rossberger, S. (1994)	UDS	Primary rat hepatocytes	98%	111.69 mM	Negative
Bolognesi et al. (1997)	DNA Damage/reactivity/ UDS	Mouse; IP administration	99.9%	300 mg/kg	Equivocal
Bolognesi et al. (1997)	DNA Damage/reactivity/ UDS	Mouse; IP administration; alkaline solution of extracted DNA	99.9%	300 mg/kg	Positive
Alvarez-Moya et al. (2014)	Comet assay	Human lymphocytes	96%[2]	700 µM	Positive
Lueken et al. (2004)	Comet assay	Human fibroblasts GM 5757	98.4%	75 mM	Negative
Manas et al. (2009)	Comet assay	Liver Hep-2 cells	96%	7.5 mM	Positive
Mladinic et al. (2009)	Comet assay	Human lymphocytes	98%	580 ug/mL (toxic); approx 3.43 mM	Positive
Rossberger, S. (1994)	DNA repair test	Male SD rat primary hepatocytes	>98%	111.69 mM	Negative
Suresh, T.P. (1992)	Rodent dominant lethal test	Male and female Wistar rats	96.8%	500 mg/kg (single dose); 100 mg/kg (5 daily doses)	Negative
Wrenn (1980)	Rodent dominant lethal test	Mouse; gavage	98.7%	2000 mg/kg	Negative
Akanuma, M. (1995)	DNA repair test (Rec- assay)	*Bacillus subtilis* M45 rec-/ H17 rec+	95.68% [2]	240 ug/disk	Negative
Li and Long (1988)	DNA repair test (Rec assay)	*B. subtilis* H17, rec+; M45, rec-	98%	2 mg/disk	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

f. Conclusions

In summary, glyphosate was not mutagenic in bacteria or mammal cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open

literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei studies considered in this assessmnt by CARC. Some positive results were reported SCE and comet assays in the open, there is no convincing evidence that the DNA damage is a direct effect of glyphosate, but rather may be a secondary effect resulting from cytotoxicity or oxidative damage.

3. Structure-Activity Relationship

At present there are no structurally related pesticide registered by the Agency which resemble glyphosate. Sulfosate (the trimethylsulfonium salt of glyphosate, also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl) glycine anion (PMG) and the trimethylsulfonium cation
(TMS). Sulfosate is classified as a Group E Chemical; "not likely human carcinogen", based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR No, 011156).

4. Subchronic and Chronic Toxicity

In a 90-day feeding study in CD-1 mice were fed diets containing 0, 250, 500 or 2500 mg/kg/day of glyphosate for three months. Body weight gains of the high-dose males and females were about 24% and 18% lower, respectively, than those of the controls. Body weight gains of the low-dose and mid-dose groups were comparable to those of the controls. Based on the reduced body weight gains in both sexes, the NOEL for systemic toxicity is 500 mg/kg and the LOEL is 2500 mg/kg. (MRID No.: 00036803).

In a 90-day feeding study in Sprague-Dawley rats were fed diets containing 0, 1000, 5000 or 20000 ppm of glyphosate for three months. These doses were equivalent to 0, 63, 317 and 1267 mg/kg/day, respectively (males) and 0, 84, 404 and 1623 mg/kg/day, respectively (females). The following findings were regarded as possibly treatment-related: (1) increased sarum phosphorus and potassium in all treated groups, males and females; (2) increased serum glucose in the mid-dose and high-dose males; (3) increased blood urea nitrogen (BUN) and serum alkaline phosphatase in the high-dose males; and (4) occurrence of pancreatic lesions in the high-dose males (pancreas was not examined at the low-dose and mid-dose groups). Based on these findings, the systemic NOAEL is < 1000 ppm (not determined definitively) for both sexes (MRID No.: 40559401).

A chronic feeding/carcinogenicity study was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 30, 100 or 300 ppm of glyphosate for 26 months. These levels were equivalent to 0, 3, 10 and 31 mg of glyphosate/kg/day, respectively, for the males and 0, 3, 11 and 34 mg of glyphosate/kg/day, respectively, for the females. There were no effects based on any of the parameters examined (toxic signs, mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology). Therefore, the NOAEL for systemic toxicity is 300 ppm (males: 31 mg/kg/day and females: 34 mg/kg/day) (MRID No.: 00093879),

A second chronic feeding/carcinogenicity study was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 2000, 8000 or 20000 ppm of glyphosate for 2 years. These levels were equivalent to 0, 89, 362 or 940 mg/kg/day, respectively, for the males and

0, 113, 457 or 1183 mg/kg/day, respectively, for the females. Treatment-related effects observed only in the high-dose group included: (1) In the females: decreased body weight gains; and (2) In the males: increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight and increased liver weight/brain weight ratio {relative liver weight). No significant systemic effects were observed in the low-dose and mid-dose male and female groups. Therefore, the NOAEL for systemic toxicity is 8000 ppm (males: 362 mg/kg/day and females: 457 mg/kg/day) and the LOAEL is 20000 (MRID No.: 41643801).

In a combined chronic toxicity/carcinogenicity study (MRID No. 49631701), glyphosate (98.9% a.i) was administered to 85 Sprague-Dawley rats/sex/dose in the diet for 104 weeks in amounts that varied in concentration to deliver 0, 10, 100, 300, and 1000 mg/kg/day to both sexes over the course on the study. Designated for the toxicity portion of the study were 35 rats/sex/dose with the remainder designated for the oncogenicity portion of the study. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of glyphosate administration.

There were no statistical differences between treated and control groups in survival rates. Pale feces were observed during weeks 16-104 in both sexes at the high dose and in females from the low-mid and high-mid dose levels. No treatment-related effect was observed in food consumption, hematology, ophthalmology, and gross pathology data. Males from the high-dose group had statistically lower mean body weight ($p \leq 0.01$) by 5% to 11% beginning Week 2 of the study until Week 104, and at termination was 10% lower (-14% weight gain). Females at the high dose had statistically lower body weight ($p \leq 0.05$) by 5% to 12% beginning Week 20 through Week 80 (with several exceptions), and at termination was 8% lower (-11% weight gain). Statistically increased ALP activities (+46% to +72%) were observed in males at the high dose throughout the study except for the 51 week interval when the mean value was 31% higher than control. Elevated ALP activities were observed in females at the high dose (+34% to +53%) throughout the study, and through most of the study at the high-mid dose by +20% to +67%, though not always statistically significant. Urinalysis data showed reduced pH (5.5-6) in males at the high dose throughout the study.

The absolute liver weight was decreased significantly in females at the high dose after 52 weeks, but after correcting for final body weight the difference was statistically significant at the three highest doses. The parotid salivary gland weight was increased significantly in males at the three highest doses (56-111%) after 52 weeks, but not after 104 weeks. The combined weight of the sublingual and submaxillary salivary glands was significantly increased by 13% (22% after correcting for body weight) at the high dose after 52 weeks. In females, the parotid gland was not affected but the sublingual and submaxillary combined weight was significantly higher by about 15%. The changes in salivary gland weights were accompanied by increased incidence of mild to severe parotid salivary gland cell alterations and slight to moderate mandibular salivary gland cell alterations were observed in both sexes at the 52-week and 104-week intervals. The lesions were described as cells and/or acini that appeared larger and stained in a weakly basophilic manner without showing a tendency toward proliferative or degenerative changes over time. In males, the increased incidence and severity of lesions in the parotid gland were significant ($p \leq 0.01$) at 100,

300, and 1000 mg/kg bw/day at 52 weeks, and significant at 300 and 1000 mg/kg bw/day at 104 weeks. The increased incidence of lesions in the mandibular gland were significant at 300 and 1000 mg/kg bw/day at 52 weeks and significant ($p \leq 0.001$) at 100, 300, and 1000 mg/kg bw/day at 104 weeks. In females, the increased incidence of parotid lesions was significant at 300 and 1000 mg/kg bw/day at 52 weeks, and significant at 100, 300, and 1000 mg/kg bw/day at 104 weeks. The increased incidence in the mandibular gland lesions was significant at the high dose at both 52 and 104 weeks. The incidence and/or severity of kidney nephropathy decreased in males at 100, 300, and 1000 mg/kg bw/day at 52 weeks and at the high dose at 104 weeks. Urothelial hyperplasia significantly decreased in females from the high dose group at both the 52-week and 104-week intervals. The LOAEL in male and female Sprague-Dawley rats administered glyphosate for 104 weeks in the diet was 100 mg/kg bw/day based on microscopic lesions in the parotid and mandibular salivary glands. The NOAEL was 10 mg/kg bw/day (MRID No. 49631701.

In another chronic toxicity/carcinogenicity study, groups of 52 male and 52 female Alpk:APSD (Wistar derived) rats were fed diets containing glyphosate at 0, 2000, 6000 or 20,000 ppm were fed for 2 years. These doses were equivalent to 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437 or 1498 mg/kg/day in females. Treatment-related finding were confined to the liver and kidneys at the highest dose (20,000 ppm). In both sexes, treatment-related changes manifested as papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria. The LOAEL was 20,000 ppm (1214 mg/kg/day in males and 1498 mg/kg/day in females) and the NOAEL was 6000 ppm (361 mg/kg/day in males and 437 mg/kg/day in females) (MRID 49704601).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

TO BE COMPLETED AFTER THE MEETING

The Committee's assessment of the weight-of-the-evidence (WOE) is discussed below.

1. Carcinogenicity in Humans

2. Carcinogenicity in Animals

3. Mutagenicity

4. Structure Activity Relationship

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

VIII. BIBLIOGRAPHY

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